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13. ABSTRACT ***(Maximum 200 Words)***

The purpose of this study was to determine whether gender, menstrual cycle phase and oral contraceptives in women affect symptoms of acute mountain sickness (AMS). The experiments consisted of 12-hr exposures to simulated altitude of 16,000 ft. Measurements of global and regional (brain magnetic resonance imaging) fluid homeostasis, ventilation, cognitive and autonomic function were evaluated in relation to baseline measurements before altitude and AMS symptoms. Subjects were 18 men and 33 women tested in both luteal and follicular phases of the menstrual cycle and when on oral contraceptives with high and low progestin dose. There were no differences in AMS severity among any of the five groups. Women have greater ventilation than men per metabolic rate, as evidenced by their lower PCO_2 at baseline and altitude, and increase their ventilation at altitude more in the luteal than the follicular phase. Women performed significantly better on cognitive function tests at baseline and altitude than men. AMS was not clearly associated with pulmonary gas exchange deterioration or altitude-induced changes in plasma volume. Brain CSF volume decreased slightly with altitude exposure, but not in relation to AMS. In general, fluid retention, with increased extracellular and total body water and reduced urine volume, tended to be directly related to AMS severity. Altitude illness did not correlate with the ventilation response to altitude or to acute hypoxic tests at baseline or to sympathetic responses at altitude, estimated from heart rate variability and catecholamines. Furthermore, responses to baseline cold pressor tests were not valid predictors of AMS. Body temperature increased at altitude and the rise correlated significantly, but inversely, with AMS. The rise in fluid-regulating hormones, ADH, aldosterone and ANP, continued in AMS-prone subjects while in a state of fluid overload.

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Jack Loppky January 24/2000

PI - Signature Date

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EXECUTIVE SUMMARY

The purpose of this investigation was to determine whether gender, phases of the menstrual cycle or oral contraceptive use by women are significant considerations in assigning military personnel to high altitude duty. In this reported study 18 healthy men and 33 women were exposed for 12 hours to a simulated altitude of 16,000 ft in a decompression chamber. Previous studies have shown that individuals who exhibit altitude sickness within the first half-day at high altitude also experience altitude sickness during the subsequent days at altitude. This chamber study was chosen because it allowed us to control and regulate the environment, activity level and food and fluid intake of the subjects and thereby also learn something about the early progression and development of this poorly understood disease. In two/thirds of the experiments the subjects experienced clear symptoms of altitude sickness, but the occurrence and severity were not different between men and women, menstrual cycle phase or the use of oral contraceptives in the repeated exposures in women.

In those subjects, men or women, who experienced altitude sickness, the concentrations of fluid regulating hormones changed differently while at altitude than in those subjects who showed no symptoms. These hormone changes, which began early during the exposure, were typical of a strong drive to retain body fluids and this fluid retention probably caused the subsequent headache and other symptoms in the subjects who became sick. This suggests that their body was responding to a shock-like reaction to the initial fall in oxygen levels, which caused instability in the regulation of blood pressure and other functions.

This large-scale study failed to reveal any differences of significance in altitude sickness that are related to gender, menstrual cycle or oral contraceptive use. Therefore, there is no reason to differentiate between men and women, cycle phase or oral contraceptive use in the assignment of military personnel to high altitude duty.

Jack Loeppky, Ph.D. January 2000

INTRODUCTION

This is the third and final report of the study entitled "The Physiology of Acute Mountain Sickness in Women." It summarizes the established methods, which were described in detail in the first report in October of 1997, and the complete results updated from those included in the report submitted in October of 1998. An abstract, essentially as submitted with the initial contract application in November of 1995, describes the overall objectives of this research:

"Women are becoming more prevalent as military personnel, but we lack basic knowledge about their physical and mental performance at high altitude. Military personnel deployed to high altitudes will be exposed to the hazards of hypobaric hypoxia and a significant number are at risk to develop acute mountain sickness (AMS). The deleterious impact of AMS on military operations has been demonstrated in both experimental studies and actual conflict. However, very few laboratory or field studies have examined AMS in women. Also, few laboratory studies have compared the responses of women and men exposed to high altitude. Thus, as more women are included in a wide variety of Army units, AMS can potentially result in a significant loss of unit strength and could jeopardize the accomplishment of a unit's mission. We are planning to study the effects of the menstrual cycle and oral contraceptive use in women on AMS and compare the results with men. The measurements for comparison will focus on AMS symptoms, fluid balance and distribution, including brain scans for cerebral edema, ventilatory and circulatory responses, autonomic nervous system function and cognitive function. In the past two years, in related studies, we have collected important data that began to address each specific aim and established that we are capable of the careful execution and analyses of the proposed study. This study will make a major contribution to the understanding of the requirements of female soldiers and other military personnel who may be exposed to high altitude."

The overall purpose, specific aims and hypotheses of the study, as stated in the initial proposal, are restated below:

The purpose of these studies is to measure the physiological responses of women to simulated high altitude during the luteal and follicular phases of the menstrual cycle, and when they are taking or are not taking oral contraceptives. We will also study a control group of men, age-matched to the female subjects in Study 1 and 2, to determine if women's responses to high altitude are different from men's. When these studies are completed the U.S. military will know whether or not women are, in general, different from men in their performance at high altitude, and at what cycle phase they perform best, and whether oral contraceptives alter their performance. The proposed studies will significantly advance our knowledge of women's responses to high altitude.

This is so even in the extreme case of finding no gender differences and no effects of the menstrual cycle or oral contraceptives on women's responses to high altitudes. The studies will also determine which physiological responses are altered in subjects developing AMS, compared to more tolerant subjects. These correlated measurements will assist in determining the cause or individual variability responsible for AMS. The proposed studies are designed to accomplish four specific aims by testing the following hypotheses.

Specific Aim 1. To determine if the symptoms of AMS are altered by the luteal and follicular phases of the menstrual cycle.

Hypothesis 1. Symptoms of AMS are reduced during the luteal compared with the follicular phase of the menstrual cycle.

Hypothesis 2. Ventilation is greater at high altitude during the luteal phase of the menstrual cycle, and results in less severe symptoms of AMS compared with the follicular phase.

Hypothesis 3. Fluid retention in response to altitude is greater during the luteal phase of the menstrual cycle, but in those with high ventilatory response fluid retention does not result in AMS.

Hypothesis 4. Increased sympathetic nervous system activity precedes fluid retention and AMS, and is independent of menstrual cycle phase.

Hypothesis 5. Cognitive impairment precedes symptoms of AMS independent of menstrual cycle phase.

Specific Aim 2. To determine if the symptoms of AMS are less severe in women taking oral contraceptives compared with the same women when they are not taking oral contraceptives (follicular phase).

Hypothesis 6. Oral contraceptives reduce symptoms of AMS.

Hypothesis 7. Ventilation is greater at high altitude when women are taking oral contraceptives and results in less severe symptoms of AMS compared to when they are not taking oral contraceptives.

Hypothesis 8. Fluid retention is reduced when women are taking oral contraceptives and results in less severe symptoms of AMS compared to when they are not taking oral contraceptives.

Hypothesis 9. Increased sympathetic nervous system activity precedes fluid retention and AMS independent of oral contraceptive use.

Hypothesis 10. Cognitive impairment will be improved in women who are taking oral contraceptives and will be associated with less cerebral edema compared to when they are not taking oral contraceptives.

Specific Aim 3. To elucidate the pathophysiology of AMS by determining its relationship with cerebral edema using magnetic resonance imaging before and after exposure to high altitude.

Hypothesis 11. Cerebral edema as determined from MRI will be greater during the follicular phase of the menstrual cycle and will be associated with more severe symptoms of AMS and fluid retention.

Hypothesis 12. Cerebral edema as determined from MRI will be greater in females not taking oral contraceptives compared to the same females when they are taking oral contraceptives and will be associated with more severe symptoms of AMS.

Specific Aim 4. To determine if significant differences in physiological responses exist between women and men when they are exposed to acute simulated high altitude.

Hypothesis 13. Women in the luteal phase of the menstrual cycle will have less severe symptoms of AMS compared to age-matched men; follicular phase will have more severe AMS.

Hypothesis 14. Women taking oral contraceptives will have less severe symptoms of AMS compared to age-matched men.

Hypothesis 15. ***Cerebral edema as determined from quantitative MRI will be the same in women with AMS compared to age-matched men with AMS.***

In the following section the above hypotheses are tested and answered.

BODY

A. Experimental Methods and Procedures

In order to give an overview of the experimental logistics, test procedures and methods that were used, we have summarized below the pertinent experimental procedures and measurements. More details are given under the results section for some measurements. Appendix 2 gives a detailed chronological list of the measurements as they were taken.

Abbreviations:

ECW: extracellular water

PV: plasma volume

TBW: total body water

D_2O: deuterium oxide

GFR: glomerular filtration rate

TCER: transcapillary escape rate

LL: Lake Louise AMS symptom questionnaire

ESQ: environmental symptoms questionnaire

elect: Na+, K+

6 hormones: epinephrine (Epi), norepinephrine (Norepi), aldosterone (ALDO), atrial natriuretic peptide (ANP), antidiuretic hormone (ADH) and plasma renin activity (PRA)

PD: plasma density

PP: total plasma protein

CPT: cold pressor test

HVR: hypoxic ventilatory response test (poikilocapnic and isocapnic)

General

The measurements times shown below assumed that the exposure on the chamber day to 426 mm Hg (=16,000 ft or 4,877m, according to West (1)) would be for exactly 12 hours. In the event that the decision was made to curtail a run, because of intolerable AMS or other reasons, the measurements or procedures scheduled for the last measurement period were started early. This schedule assumed that 3 hr were required for the ECW-NaBr test (one sample after 3 hr) and 3 hr were required for TBW-D_2O (one sample after 3 hr) and that at least 30 min were needed for the PV-Evans blue test (3 samples at 10 min intervals) and that TCER from Evans blue could be obtained from a 3-hr slope of Evans (3 early samples and additional samples after 1, 2 and 3 hr). It was also assumed that fluid intake equaled urine output after time zero and subsequent intake was matched to output of the previous 3-hr interval. GFR was estimated from creatinine clearance. Respiratory measurements were made with an automated system (Consentius Technologies, Sandy, Utah) with incorporated software. Measurements included total ventilation ($\dot{V}_E$), oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), respiratory exchange ratio (R) and other calculated variables. End-tidal O_2 and CO_2 ($P_{ET}O_2$ and $P_{ET}CO_2$), assumed equal to mixed alveolar values (2), were measured separately from the breathing valve (Hans Rudolph, model 2600) with an MGA -1100 mass

spectrometer (Marquette). Arterial samples were obtained from single femoral artery punctures during the respiratory measurements on the control day and during the first and last hour at altitude. Arterial blood measurements included $PaCO_2$, PaO_2, saturation (SaO_2), pHa and hemoglobin (Hba), all measured on a Radiometer (model 520) blood gas analyzer. Peripheral venous blood hemoglobin (Hbv) was measured on an OSM-3 Hemoximeter (Radiometer, Copenhagen) and venous hematocrit (Hct) was obtained by standard micro-hematocrit method.

The serial results for measurements have been generally designated as C12 (late afternoon-early evening on the control day), A0 (just prior to entering the chamber on the altitude day) and A1, A3, A6, A9, A12 on the altitude day, which correspond approximately to the number of hours at altitude. A12 and C12 represent measurement times at approximately the same clock time on successive days.

TIME OF MEASUREMENTS

Day 1: Control day, Day 2: Altitude day

Weight: Day 1: 7:00 PM

Day 2: 7:00 AM, 10:00 AM, 1:00 PM, 4:00 PM, 7:00 PM

Body Temp: Day 1: 7:00 PM

Day 2: 8:00 AM, 1:30 PM, 7:00 PM

HVRs: on control day afternoon

3-breath tests: on control day afternoon and after 1, 6, and 12 hr in chamber

Maximal Exercise: before control day

Cold pressor test: on control day afternoon

Respiratory (ventilation)

Day 1:	Day 2:
6:30 PM + arterial blood	8:30 AM (1) + arterial blood
	1:30PM (6)
	6:30 PM (12) + arterial blood

Symptoms (LL)

Day 1:	Day 2:
2:30 PM (practice)	6:30 AM (0)
6:00 PM add ESQ	8:00 AM (1) add ESQ

1:00 PM (6) add ESQ
6:00 PM (12) add ESQ
8:30 PM, Post MRI

Heart rate & blood pressure

Day 1:	Day 2:
6:30 PM	8:30 AM (1)
	1:30 PM (6)
	6:30 PM (12)

Cognitive testing

Day 1:	Day 2:
2:00 PM (practice)	8:30 AM (1)
6:30 PM	1:30 PM (6)
	6:30 PM (12)

Spirometry

Day 1:	Day 2:
6:30 PM	8:30 AM (1)
	1:30 PM (6)
	6:30 PM (12)

Fluids:

1) TBW (D_2O) Day 1: Drink 4:00 PM - sample 6:00 and 7:00 PM
Day 2: Drink 4:00 PM - sample 6:00 and 7:00 PM

(2) ECW (NaBr) Day 1: Drink 4:00 PM - sample 6:00 and 7:00 PM
Day 2: Drink 4:00 PM - sample 6:00 and 7:00 PM

(3) Plasma Volume (Evans) Day 1: Inject 4:00 PM- sample 4:10 PM, 4:20 PM, 4:30 PM
Day 2: Inject 4:00 PM- sample 4:10 PM, 4:20 PM, 4:30 PM

(4) TCER (Evans) Day 1: Inject 4:00 PM- sample as above plus 5:00, 6:00 PM, 7:00 PM
Day 2: Inject 4:00 PM- sample as above plus 5:00, 6:00 PM, 7:00 PM

(5) Urine (volume) and intake:

Day 1:	Day 2:
6:00 AM void and balance	5:00 AM void and balance
4:00 PM void and drink	7:00 AM void and drink
7:00 PM (collect)	10:00 AM (collect, 0-3) and drink
	1:00 PM (collect, 3-6) and drink

4:00 PM (collect, 6-9) and drink

7:00 PM (collect, 9-12) and ad lib intake

Albuminuria, urine elect, osmol and creatinine for GFR

Day 1:	Day 2:
7:00 PM	10:00 AM (1)
	1:00 PM (6)
	4:00 PM (9)
	7:00 PM (12)

Venous blood: creat (for GFR), elect, PP, osmol, PD, Hbv, Hct, 6 hormones, extra plasma

Day 1:	Day 2:
6:00 PM	
	6:30 AM: PD, Hb, Hct, osmol, 4 hormones-after study began (0)
	8:30 AM (1)
	1:00 PM (6)
	6:00 PM (12)

Venous blood: progesterone Day 1: 7:00 AM Day 2: 6:00 AM

Venous blood: Epi, Norepi Day 1: taken before and during last min of CPT.

Subjects

The subjects were selected from volunteers who responded to advertisements in the local area. Those expressing interest, after being given a description of the study, were further selected based on availability for scheduling, medical screening and routine biochemical laboratory screening. A subject's prior experience at altitude was noted, but was not considered in subject selection. If screening results were satisfactory, subjects were enrolled in the study for preliminary practice testing. Occasionally scheduling conflicts developed and in a few cases it was found that some women had unexceptible blood progesterone levels and were excluded from the study. Some did not have adequate progesterone surges in the luteal phase and some had elevated progesterone levels while on oral contraceptives. Two women with low blood iron (Fe/TIBC<15%) were given iron supplements to correct the deficiency.

Of the 51 subjects chosen for the study (18 men and 33 women), 34 were undergraduate or graduate students in various diciplines at the University of New Mexico. The

others included five medical laboratory technicians, four teachers, four field biologists, two computer programmers, one medical technologist and one artist.

All data reported here were collected from April/1997 through January/1999. During that time 102 complete experiments (altitude exposure/person) were performed. During each altitude chamber experiment there were one, two or three subjects exposed at the same time. With more than one, the starting times of the experiments in the chamber were appropriately staggered to prevent subsequent delays at the MRI facility following each subject's exposure. On four occasions three subjects were tested on the same day, 24 times two subjects were exposed at the same time and on 42 days only one subject was exposed to simulated altitude. The 102 experiments included:

a) 18 men (one repeated because of MRI malfunction), total = 19 experimental runs,

b) 19 women were tested during both menstrual phases and another two women in the follicular phase only (the latter two were not available for testing in the luteal phase), total = 40 runs,

c) 20 women taking oral contraceptive pills (OCPs) were studied twice, once on the last day or second last day of their pill week (highest progestin level) and once during the last few days of their placebo week (lowest progestin level). Another female was tested during her pill week only (not available during her placebo week), total = 41 runs.

d) One woman of the latter group was tested during her pill and placebo week, but subsequent to her runs, her endogenous progesterone was found to be elevated, most likely because she had not been on OCPs a sufficient length of time. The data from these two runs was not included in the database, as she subsequently repeated these OCP runs.

Nine of the women completed four runs, the follicular and luteal runs during their normal menstrual cycles and the placebo and pill runs while on OCPs. One of the women completed her OCP runs first, followed by her menstrual cycle runs after having been off OCPs for 4 months. The other eight completed the menstrual runs first and then the OCPs. One was on OCPs for 5 months prior to her first OCP run and the other eight were on OCPs for 3 months before their runs. The other 11 OCP subjects who only took part in the OCP runs had been taking oral contraceptives for times ranging from 6 months to 8 years.

Determination of menstrual cycles

The projection of menstrual cycle (follicular and luteal) phase dates for scheduling experiments was accomplished by a combination of interviews, previous dates of menses and

daily recording of oral temperature (taken in the morning). When the calendar dates of cycles were established the subject was tentatively scheduled one or more months in advance. The projected date of the luteinizing hormone (LH) surge was confirmed with an LH kit by the subject during the previous or current cycle (6-day kit, OvuQuick 1-step, Conception Technologies, San Diego, CA). The date of elevated progesterone in the luteal phase was usually confirmed in the luteal cycle before the cycle during which experiments were done by blood progesterone assays. The control day (preceding the chamber day) for the luteal cycle was scheduled on about the 4th day following the LH surge, depending on subject's cycle length and blood progesterone levels measured periodically in weeks preceding the experiments. A blood progesterone level of at least 6 ng/ml defined the luteal phase. The progesterone values shown in Table 1B and 1C-appendix for the women subjects are the average of values measured on the control and altitude days to confirm cycle phase. Blood progesterone was measured using a microparticle enzyme immunoassay (MEIA) technique (Abbott) at the Lovelace Clinic Laboratory under the supervision of Dr. L. Gates.

Of the 19 women who were tested in both parts of the cycle, 11 were tested first in the luteal phase and eight were tested first in the follicular phase. The average time interval between experiments for each of these 19 women was 6 weeks (range: 2-28 weeks).

Experimental schedule of women on oral contraceptives (OCP)

Women taking OCPs were studied once near the end of the "control" week when on the placebo pill (C) and once near the end of the week when they received the highest progestin level pill (the third week of the pill cycle, for both monophasic or triphasic pills). Of the 20 women who were tested twice on OCPs, 12 were tested first during the pill week (P) and eight were tested first during the placebo week. The average time interval between experiments for each of these 20 subjects was 4 weeks (range: 1-12 weeks).

The specific types of contraceptives taken by the 21 women were prescribed by their personal physicians and no attempt was made to influence this choice by the investigators. The OCPs taken by these subjects can be generally characterized as follows: nine women took triphasic pills and 12 took monophasic pills. In all but one, the exogenous estrogen was ethinyl estradiol, with the dose ranging from 0.03-0.04 mg. One subject (#47) took an OCP that did not contain estrogen. The exogenous progesterone (progestin) was most commonly norgestimate, but desogestrel and norethindrone were substituted in approximately one-third

of the women. The progestin doses ranged from 0.15-0.50 mg, including the variations in dose for those women on triphasic pills.

Methods for Plasma Measurements of Fluid-regulating Hormones

These were measured under the supervision of Dr. H. Hinghofer-Szalkay at the Department of Physiology, University of Graz, Austria.

ADH: Arginine vasopressin (AVP) was determined in ethanol-extracted plasma using RIA (Nichols Institute, Diagnostics BV, The Netherlands) with I^{125}-Vasopressin as the labeled compound. The anti-AVP antiserum does not cross-react with Lys^{8}-Vasopressin, oxytocin or vasotocin. Sensitivity was 0.6 pg/ml, determined as 2 SD below maximum binding.

ANP: ANP was determined with an RIA kit without prior extraction (Nichols Institute, Diagnostics BV, Netherlands). Sensitivity, defined as the apparent concentration at 3 SD from the counts at maximum binding, was 11 pg/ml.

ALDO: Aldosterone measurements were done via modified RIA (AldoCTK-2, Sorin Biomedica, Italy). Sensitivity, defined as the apparent concentration of analyte that can be distinguished from the zero standard, was below 20 pg/ml at the 95% confidence limit. The coefficient of variation for the within- and between-assay variability was 9.7 and 11.5%, respectively.

PRA: Plasma renin activity was determined by quantitative measurement of angiotensin-I (RENCTK, Sorin Biomedica, Italy). The principle of the RIA is based on the competition between labeled angiotensin-I and angiotensin-I contained in probes to be assayed for a fixed number of antibody binding sites. PRA is expressed in terms of the number of nanograms of angiotensin-II formed per ml of plasma after a one hour incubation period (ng/ml). Sensitivity, the amount of analyte able to lower the binding ability by 2 SD, was 0.13 ng/ml; the coefficient of variation for the within- and between-assay variability was 7.6 and 9.1%, respectively.

Blood samples were obtained via indwelling venous cannula from the arm. Blood was drawn by syringe and placed in glass tubes containing EDTA. These samples were then placed on iced water and centrifuged within 10 min at 4°C for 20 min. Plasma was separated, placed in cryo-tubes and placed on dry ice. At the end of the day these frozen samples were transferred to a freezer, maintained at -80°C, until shipment on dry ice.

Methods for Measurements of Plasma Catecholamines (Epi, Norepi)

These analyses were performed at Walter Reed Hospital, under the supervision of Dr. G. Kamimori.

Isolation of catecholamines from human plasma was accomplished by alumina extraction using a Chromsystems reagent kit (Alko Diagnostics, Holliston, MA). Once extracted, plasma catecholamine concentration was quantified by high performance liquid chromatography (HPLC). The Waters (Waters Corp.,Milford, MA) HPLC system consisted of a pump (model 510), WISP auto-injector (model 712) with cooling module, column oven and an electrochemical detector (model 460). Data was stored and analyzed using the Waters Millennium software package (V 2.10). The flow rate was 0.8 ml/min, column oven was maintained at 40°C, samples in the auto-injector were maintained at 4°C and the column was a 15 cm reversed phase C-18 with 5µm silica particles.

Quantification of catecholamine concentrations is based upon the comparison of the ratio of the norepinephrine peak area to the peak area of the internal standard, DHBA, within an unknown sample. This ratio is then compared to the same ratio in the plasma standard. The determination of the amount of epinephrine in the unknown sample is based on a similar comparison. Using the information obtained from the standards, and these ratios, a regression line is generated to obtain the sample areas for the other unknown samples. The assay sensitivity is 5 pg with a signal-to-noise ratio of 5 to 1 and a between days coefficient of variation of less than 3%. The within-days variation is less than 1% and the standard curve for the range of 5 to 5,000 pg has a correlation coefficient of 0.9989. In nearly all plasma samples an endogenous plasma peak appears between the EPI and DHBA peaks. This substance is hydrocaffeic acid and does not interfere with the analysis. After the DHBA peak, one may see a negative peak on the chromatogram. Like the plasma peak, this peak does not interfere with the analysis.

The blood samples for plasma catecholamine analysis were obtained from subjects by indwelling venous cannula, previously placed in an arm vein and maintained patent by periodic infusion of physiological sodium chloride solution. All samples were drawn after a minimum of 30 min of complete semi-recumbent rest, with noise and light minimized and eyes closed. For each 5 ml sample of blood, 20µl of the following stabilizing solution was previously added to chilled heparinized vacutainers: 900 mg EGTA (ethyleneglycol-bis-(b-aminoethylether) N, N, N, N-tetraacetic acid), 750 mg GSA (glutathione) in 10 ml bidistilled water. The test tube with the blood sample was gently inverted a few times to ensure adequate mixing of blood with the stabilizing solution. The test tube was placed in an ice bath and within 10 min centrifuged for 20 min at 4°C. After centrifugation, the plasma was placed in a refrigerator and then placed in a freezer at -80°C until shipment under dry ice and subsequent analysis.

B. Results and Discussion

The basic assumption for this study was that as subjects develop symptoms of acute mountain sickness (AMS), the progressive severity over the 12 hr at altitude would correlate with some of the variables measured during the course of the altitude exposure, thus helping to explain the pathophysiology. In most cases comparisons were made between the last altitude measurement (A12) during the last or 12th hr and the control measurement (C12) the day before. The maximum oxygen uptake measured during the exercise test (usually performed some days before altitude exposure), the autonomic responses to the cold pressor test and the ventilatory response measurements taken on the control day were also considered in regard to their validity in predicting subsequent AMS for the subjects, based on the resulting correlations with subsequent AMS severity.

Presented below are the measurement data of variables that have previously been implied to be important in the occurrence of AMS. Measurements were analyzed locally at the altitude chamber at the University of New Mexico, in the LRRI laboratory, at the VA Medical Center (MRIs) or at the Lovelace Clinic Laboratories. Off site analyses included catecholamines by Dr. Kamimori at Walter Reed, NaBr and D_2O for water compartments by Metabolic Solutions in New Hampshire and aldosterone, atrial natriuretic peptide, antidiuretic hormone and plasma renin activity by Dr. Hinghofer-Szalkay at the University of Graz, Austria.

The following data sections follow a similar format, in that they present the results of the measured variables by subgroups and in association with AMS severity.

Missing data will be noted in some of the tables of raw data for individual subjects. This occurred for numerous reasons and is not unexpected in a study of this type and magnitude. Occasionally data was not obtained because of malfunctioning equipment during the experiments or during subsequent laboratory analyses. Often measurements were not made because choices needed to be made between performing the measurement and the subject's comfort or choosing between two measurements when time or the technicians' ability to perform both was limited. This occurred more frequently when more than one subject was studied simultaneously. Occasionally venous catheters would become non-patent and insertion of another seemed an extra hardship on the subject. Arterial sampling was not trivial under these conditions and occasionally these were not completed in the time allotted for them or they were omitted because of concern for the subject's psychological and physical tolerance. Acute altitude hypoxia caused mood and personality changes in some subjects and

measurements that were tolerated well during control conditions became an ordeal at altitude. Under the circumstances of the study, the research team performed admirably and can be proud of a job well done.

AMS Symptom Scores

The subjects were placed on a gas mixture containing 13.7% O_2 from the time that they left the altitude chamber until they entered the MRI facility. This transport time was approximately 15 min. When moderate or severe AMS developed during the 12-hr chamber exposure, significant AMS was usually still present following the MRI scan, approximately one hour after the subjects had been in a normal oxygen environment. We believe that during these 12-hr chamber exposures the subjects exhibited true symptoms of AMS. A recent publication (3) has indicated that AMS symptoms occurring in an acute 9-hr chamber exposure are closely correlated with symptoms occurring in longer-term exposure to actual high altitude.

In Tables (1A, B and C-appendix) the Lake Louise scores are given as recorded by the subject just prior to entering the chamber (A0) and after one hr (A1), six hr (A6) and during the last or 12th hr (A12) in the chamber. In 80% of the chamber experiments the subject remained in the chamber from 11 to 12 hr. In 20 runs the exposures were terminated between seven and 11 hr because the subject's AMS symptoms were too severe to warrant continuation of the experiments in terms of data validity and subject safety and tolerance for further testing. A final Lake Louise AMS score was obtained after A6 in all but two cases and this is denoted subsequently as A12. For the two cases, the value at A6 has also been entered in A12.

In the first two reports we utilized the average Lake Louise (LL) scores at A6 and A12 as the AMS severity index with which to correlate other physiological measurements. For this final report, the results of the environmental symptoms questionnaire (ESQ) were also available. This test was done on a keyboard a few minutes after the Lake Louse scores were obtained. A subset of 11 of these 67 questions are similar or closely related to the LL questions and are known as the AMS-C (cerebral) score. This sub-score of the ESQ has been found to correlate closely with the LL score in previous studies (4). Because AMS is a subjective self-evaluation by the subject, it was decided that the validity of the final "peak" AMS score would be improved if it was based on both the LL (maximum score = 12) and the

AMS-C score (maximum score = 5) from the ESQ. In order to obtain this average "peak" AMS score for each run the following steps were taken:

1) The "peak" LL and AMS-C score were recorded as the score at A12 in the majority of the cases, or as the average of A6 and A12 when the A6 score was higher than the A12 score (as occurred in 15 of the 100 runs).
2) From these two peak scores any corresponding values greater than zero that were recorded during the baseline (control) testing the day before (C12) were subtracted. For the LL score, any baseline value above zero was subtracted from the same category of the peak score. A score greater than zero at C12 occurred in 30% of the cases.
3) A least squares linear regression line was computed between these "corrected" AMS-C (X) and LL (Y) values. The result is shown in Fig. 1 for 98 cases (in two cases AMS-C scores for corresponding LL scores were not recorded and only the LL scores were used). The equation is: $Y = 1.169 + 2.327X$, $r = +0.84$, $P<0.001$.

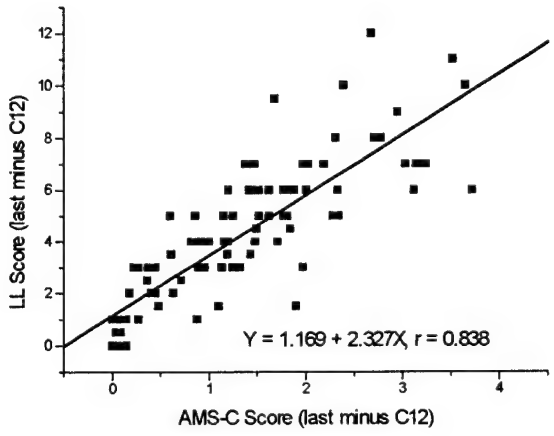


Fig. 1. Peak LL and AMS-C scores in 98 subjects.

4) The LL scores for each subject predicted from the equation were then averaged with the actual recorded LL score. This average score, giving equal weight to the LL and ESQ scoring systems, is hereafter referred to as AMSa and has been entered in Tables 1A, B and C-appendix. This value is utilized in all subsequent comments pertaining to AMS.

The equation shown above indicates that LL scores of 3 and 2 correspond to AMS-C scores of 0.8 and 0.4, respectively. Because a score of 0.7 on AMS-C has been associated with the presence of AMS by others altitude investigators (5), we have now revised our criterion for the presence of acute mountain sickness from earlier reports. We now consider

AMS to be present when the LL and AMSa score is 3 or higher (including a headache of 1 or more), instead of 2 or higher.

Body Fat, $\dot{V}O_2$max and AMS

The lean body mass (LBM) was estimated from total body water (TBW) obtained from the D_2O measurements (6), according to the laboratory where these analyses were performed (Metabolic Solutions, Nashua, NH). The equation is LBM = TBW / 0.72 and percent body fat (%fat) was calculated as ((body wt – LBM) / body wt) X 100. The average values for the control and altitude days was used for subjects who were only tested once and in those tested two or 4 times, all pairs of these values were averaged.

It has been suggested that endurance fitness and body fat may be related to altitude tolerance. These measures were evaluated by linear correlation for the 51 subjects. For this purpose, the AMSa values were averaged for those subjects who completed more than one experiment. As expected, a significant negative correlation was obtained for $\dot{V}O_2$max/LBM and %fat (n = 51, r = -0.41, P = 0.003). However, neither %fat (r = +0.19, P = 0.17) nor $\dot{V}O_2$ max/LBM (r = -0.13, P = 0.36) correlated significantly with AMSa, demonstrating that susceptibility to AMS is determined by factors other than endurance fitness or body composition.

Tables 1A, B and C-appendix show the mean for age, $\dot{V}O_2$max, %fat, $\dot{V}O_2$max/LBM, actual LL AMS symptom scores and the calculated AMSa obtained on the 18 men. Their mean age was 27.4 (SD = ±3.2) yr, very similar to that of the 33 women 27.2 (±4.5). The $\dot{V}O_2$max for the men was 47 (±8) ml/min/kg, measured on a ramp protocol on an exercise ergometer, and was significantly higher (P<0.001) than in the 33 women (36 ±7). All values are equal or greater than those previously reported for healthy sedentary individuals (7). The %fat for the men averaged 13 (±6) and in the women it was significantly (P<0.001) higher at 28 ±7. Because the greater %fat in the women resulted in a relatively smaller LBM for them, the $\dot{V}O_2$/LBM values were not significantly different between the men and the women (54 ml/min/kg for the 18 men and 49 for the 33 women).

Order effect

In subjects exposed to altitude on two or more occasions, the first trial might have been expected to result in higher AMS scores because of unfamiliarity and apprehension of the environment and associated symptoms in those subjects not having experienced AMS before.

In order to determine whether the test order altered the resulting AMSa values, we compared AMSa values between the first and second trial in the 31 subjects taking part in two or more trials (one male, 18 menstrual cycle runs and 12 OCP runs). The mean AMSa value on the first trial was higher by an average of 0.67, but this difference was not significantly different from zero ($0.1<P<0.2$). Twelve of the 31 subjects had higher scores on their second trial. The test order is therefore ignored in subsequent considerations of the women's data.

Men: The mean AMSa was 4.17 (Table 1A-appendix) and demonstrated the expected variation among individuals (coefficient of variation-CV= 70%). The LL scores show the essentually linear increase from the first to the last hour at simulated altitude. Based on the minimum criterion of a total score 3, with a headache of 1, as determining the presence of AMS (4), 11 of the 18 men had AMS (61%) and 7 did not. The average of the peak headache score (highest value at hr 6 or last hr) was 1.7.

Women during follicular and luteal phase of menstrual cycle: Nineteen women were studied twice during their two menstrual phases. One of these subjects completed two runs on oral contraceptives prior to these tests. Eleven were studied first in the luteal phase (L) and eight were studied first in the follicular phase (F). Two additional women were studied only in F. The results for AMSa are shown in Table 1B-appendix. During F, 11 of the 21 women (52%) had AMS by the above criteria and 12 of the 19 (63%) had AMS during L.

In order to compare AMSa results between men and women's subgroups and between the latter, the statistical results are presented in the table on the next page in three ways. First, as a paired comparisons between the nine women who took part in all four conditions (common, lower left center), secondly, as an ANOVA analysis between all subjects of each group, which ignores the fact that some of the subjects were paired (upper right center) and thirdly, as paired comparisons between F and L (n = 19) and between C and P (n = 20) for those women that took part in each pair.

Statistical comparison of AMSa scores between men and women's subgroups.

	Group Total			9 Common Paired-t \ **PROB** \ Group ANOVA				All-paired		
	n	Mean	SD	Foll	Lut	C	Pill	n	Mean	SD
Men	18	4.17	2.93	0.85	0.54	0.94	0.69			
Foll	21	4.35	2.75		0.37	0.89	0.84	19	4.24	2.84
								P=0.38		
Lut	19	3.67	1.87	0.09		0.40	0.19	19	3.67	1.87
C (plac)	20	4.24	2.23	0.24	0.15		0.70	20	4.24	2.23
								P=0.64		
Pill	21	4.50	2.03	0.25	0.22	0.90		20	4.43	2.06

Including all subjects, the mean value of 4.35 for F was not significantly higher than the 3.67 value for L (P = 0.37), with a mean peak headache of 1.4 and 1.2, respectively. In the 19 paired runs, the average AMSa for F was 4.24. The difference in AMSa was again not significant, using a paired t-test and two-tailed significance levels, with about the same probability level (P = 0.38). The correlation between the 19 pairs of subject runs for L and F was not significant (r = +0.35, P = 0.14), indicating that the AMSa variation within subjects was not significantly related to the menstrual cycle. The first hypothesis can now be addressed:

Hypothesis 1. Symptoms of AMS are reduced during the luteal compared with the follicular phase of the menstrual cycle. This hypothesis is rejected. Although the mean AMSa was 15% lower in L in women taking part in both F and L, the difference was not significant when using any of the three statistical tests.

Women on oral contraceptives: Twenty women were studied twice while on OCPs, once during the placebo run when the progestin dose was zero (C) and once on the pill dose (P). Eight were studied first during C and 12 were studied first during P. One was tested only during P. The results for AMSa are shown in the table above. During C, 12 of the 20 women (60%) had AMS by the above criteria and 16 of 21 (76%) had AMS during P, with mean peak headache scores of 1.7 and 1.6, respectively. In the 20 paired runs, the average AMSa for C was 4.24 and 4.43 for P. No significant difference in AMSa was found between C and P by any of the statistical tests. The P values were 0.70 by group ANOVA, 0.64 in the 9 common subjects by paired-t and 0.64 for all 20 pairs. The correlation between the 20 pairs of subject runs was significant (r = +0.62, P = 0.004), indicating that the relative AMSa scores in these exposures remained unchanged.

Men vs. women and women's subgroups: From the table on the previous page, the average AMSa of 4.17 for the18 men is not significantly different from values in the women's subgroups, ranging from 3.67 to 4.50 (lowest P=0.54). Also, the mean AMSa in all the women (4.20) is very similar to that of the men. The13th hypothesis can now be answered:

Hypothesis 13. Women in the luteal phase of the menstrual cycle will have less severe symptoms of AMS compared to age-matched men; follicular phase will have more severe AMS. Both parts of this hypothesis are rejected. Although the mean AMSa was 12% lower in L than in men, this difference did not approach statistical significance (P = 0.54). Secondly, Although the AMSa was 4% higher in F than in the men, the P-value of 0.85 indicates that this difference is trivial. The 14th hypothesis can also be answered:

Hypothesis 14. Women taking oral contraceptives will have less severe symptoms of AMS compared to age-matched men. This hypothesis is rejected. Both groups of women taking oral contraceptives had mean AMSa scores that were higher than in the men, although the P-values of 0.94 for C and 0.69 for P do not support these higher values in the women. The 6th hypothesis can also be addressed:

Hypothesis 6. Oral contraceptives reduce symptoms of AMS. This hypothesis is rejected, based on the values in the statistical table on the previous page. The mean AMSa in the two groups of women taking OCPs was higher (4.37) than in the women not taking them during L and F (4.03). The mean score in F was 4.35, essentially identical to the average for the two OCP experiments.

The ANOVA comparisons between F vs. L and between C vs. P agree closely with the paired-t test results in supporting no difference in these groups. In the results of the nine common subjects, these findings are supported, but the P values in the above table are lower. The mean values for AMSa for F, L, C and P were 5.26, 3.58, 4.11 and 4.18, respectively, showing that AMSa during F tends to be higher than in the other three conditions and during L tends to be the lowest. However the only P value approaching significance was 0.09 when comparing F vs. L.

In summary, these results indicate that there is no significant difference between men and women in their susceptibility to AMS as measured by AMSa. There is also no difference in AMS between menstrual cycle phase. Furthermore, AMS is not altered by taking OCPs or related to acute variations in progestin levels when taking OCPs.

Dietary Control and Results

Prior to any testing, subjects were asked to provide a 3-day diet record for days on which they felt well and that they considered representative of their usual eating pattern (i.e. not holidays). Subjects were instructed on how and what to record, including type of food preparation, quantity and condiments. Records were clarified if, upon nutrient analysis, total calories averaged less than 25 kcal/kg of body weight. If so, then subjects were requested to submit a second 3-day record after receiving an explanation that the previous record appeared to have missing data. The second record was then accepted as normal intake.

Nutrient analysis was conducted using the Nutrition Analysis Tool (v1.1) created by the Department of Food Science and Human Nutrition at the University of Illinois, based on USDA Handbook #8 and provided via www.ag.uiuc.edu/~food-lab/nat/. Average intake reported for the 3-day period was designated as the intake goal. Foods were selected for each subject to provide 90% to 110% of their reported average intake (designated goal) for calories, protein, fat, sodium and fiber. The foods utilized in this study were commercially available nutrient supplement beverages, enriched sports bars, packaged snack crackers and cookies, fruit juices, frozen dinners and canned soups. Care was taken to accommodate food preferences, i.e. vegetarian meals, no cheese, no chile. One caffeine-containing beverage per day was included for individuals habitually drinking coffee, tea or colas. Label values for nutrients were utilized to estimate amounts provided for calories, protein, fat, sodium and fiber. Amount of carbohydrate provided was calculated by the following formula:

Carbohydrate in g = (total calories – protein in g X 4 – fat in g X 9) / 4

The intake goal and percent provided for each of these nutrients is listed in Tables 2A, B and C-appendix.

Subjects were provided menus matched to their own average intake and food preferences on the control day (the day prior to the chamber day at simulated altitude) and the chamber day (at altitude). Foods for each subject were identical on these two days, but were different between subjects, based on individual goals and preferences. Records were kept of food not eaten and the nutrient value of that uneaten food was subtracted from the total food provided for the 24 hr on the control day to give the value for each individual of food eaten in the 24-hr control period. This value was divided by the goal intake to indicate percent of intake goal eaten on the control day and designated as %eaten. Values for %eaten for each subject are listed in Tables 2A, B and C-appendix.

The food intake on the chamber day was similarly determined by subtracting the nutrient values of foods not eaten from that provided. The food supplied during the chamber

day did not include the dinner supplied on the control day. Therefore, the nutrients eaten on the chamber day were subtracted from nutrients eaten during the same time period on the control day. The result was divided by nutrients eaten during that time period on the control day to calculate the percent change in nutrients eaten during altitude exposure. Records of foods eaten from four individual altitude tests (two luteal, one follicular and one placebo) were not available for analysis and therefore no nutrient data from those tests were included in the tables. Values for percent change in nutrients eaten at altitude for each subject are listed in Tables 2A, B and C-appendix.

Results: In their 3-day dietary records, the 18 men reported eating 33 ± 2 kcal/kg body weight (mean ± SE) and the 33 women reported eating 32 ± 1 kcal/kg body weight. The normal intake for moderately active men and women is 37 and 36 kcal/kg of body weight, respectively (8). This indicates that the food records provided by the subjects were reasonable, at about 90% of that recommended (9). The approximately 7% lower consumption of total calories on the control day compared with the average intake goal, suggests that the total energy provided in the study was sufficient and similar to usual intake. The average percent of goal intake for calories that was provided for consumption was 106±1% for both men and women. On the control day, %eaten of the intake goal for total calories was 103 + 2% for men, and for women in follicular phase, luteal phase, on the placebo pill and the highest progestin pill, the values were 96 ± 3%, 92 ± 5%, 89 ± 7% and 93 ± 3% respectively. The relatively high variability during the placebo phase was due to three women who ate very little on either the control day or the chamber day during these trials.

The decline in calorie intake due to altitude was 25%, 17%, 34% and 24% for women during the follicular, luteal, placebo and pill experiments, respectively. For men the decline in energy intake was 14%. Each reduction was significantly different from zero ($P<0.04$). However, there was no statistical difference by ANOVA of the decline in intake between the five groups ($P = 0.28$). The average decline in caloric intake was somewhat less than the 38% decline reported by Hannon et al. for 8 female students, age 18-23 yr, during the first 24 hr at 4,300 meters on Pikes Peak (10). For all subjects, the decline in energy intake was related to the AMSa score, $r = -0.42$, $n = 95$, $P< 0.001$. Correlation coefficients for the individual groups are presented in the table on the next page.

Relationship between change in caloric intake at altitude and AMSa.

	r	n	P
Follicular	-0.56	20	**0.010**
Luteal	-0.35	17	0.17
Placebo	-0.47	19	**0.044**
Pill	-0.28	21	0.21
Male	-0.61	18	**0.008**

The differences in intake for the other nutrients in Tables 2A, B and C-appendix are generally similar to the findings quantified above for total calories.

Cold Pressor Test and AMS

The cold pressor test (CPT) was given to the subjects on the control day preceding their altitude trial. It consisted of placing a lower arm (to the mid-bicep) into ice water for 5 minutes. The subject was asked to rate the pain on a 10-point scale each minute. Systolic and diastolic blood pressures and heart rate (HR) were measured before and during each minute of the test from the opposite arm with an automatic sphygmomanometer. Mean blood pressure (MBP) was calculated from these readings as ((2 X diastolic) + systolic)/3. Also, blood samples were taken from an intravenous cannula in the opposite arm just before the arm was placed in the ice water and at the end of the 5-min test. These samples were subsequently analyzed for epinephrine (Epi) and norepinephrine (Norepi).

The purpose of the CPT was to determine whether the conditions of the study (gender, menstrual cycle phase and OCPs) altered the measured autonomic (sympathetic) responses of the subjects to this acute stimulus. Variations in intensity of the sympathetic response to the stress of altitude have been implicated in determining the severity of AMS. Therefore, we estimated the relationship by calculating correlation coefficients between these CPT changes and the AMSa measured at altitude the next day in order to determine whether these acute measures during a CPT might have a predictive value for AMS.

In response to the test, the peak change (Δ) for pain, HR and MBP occurred most often in the second minute. The average peak changes in the five measurements, regardless of when they occurred, are given in the table on the next page. This table shows the mean changes for each of the five measurements for all runs combined and the r-values and

probability of statistical significance of the r-values from linear regressions between these responses and AMSa. It also shows the relationship between each of the five measurements combining all runs.

Relationship between CPT responses and AMSa

	Mean	SD	n	AMSa	ΔNorepi	ΔEpi	Δpain	ΔHR	ΔMBP
AMSa	4.19	2.35	99		0.76	0.84	0.82	0.81	0.25
ΔNorepi	190	452	99	0.03		0.42	0.76	0.77	0.19
ΔEpi	-12	312	97	0.02	0.08		0.19	0.46	0.95
Δpain	6.4	2.4	98	-0.02	0.03	0.13		0.20	0.14
ΔHR	16	15	99	0.02	0.03	0.08	0.13		**0.004**
ΔMBP	23	11	99	-0.12	0.13	0.01	0.15	0.29	

r values: lower left-center; P values for r: upper right-center

The MBP and HR increased by 23 mm Hg and 16 bpm, respectively, and Norepi increased 190 ng/ml and Epi decreased by 12 ng/ml, both with large scatter. The mean perceived pain rose from 0 to 6.4. The only trend noted for an association with subsequent AMSa was for ΔMBP (P = 0.25), where a greater rise in MBP during the CPT was associated with a lower AMSa (r = -0.12). All five measurements made during the CPT have previously been associated with a generalized sympathetic response, however, the only pair of measurements that were significantly related with each other were ΔMBP and ΔHR (n = 99, r=0.29, P = 0.004).

The individual responses for each subject are given in Table 3-appendix and statistical comparisons for the five measurements in the subgroups are given in Table 4-appendix. Table 4-appendix shows that Norepi increased most in C, closely followed by the men, and it was lowest in F. The only significance (P = 0.05) noted was in the 9 subjects who performed all four trials, wherein the increase in Norepi was greater in L than in F. However, the significance of this finding can be disputed because the paired-t test on the 19 women who performed both of these runs did not show a significant difference (P = 0.16). None of the individual group Norepi values were significantly associated with AMSa.

For ΔEpi, the results in Table 4-appendix also show a large mean difference between groups, ranging from 38 ng/ml in L to –75 in C, but again because of the large variability

between subjects, no significant differences are noted. In the relationship with AMSa, the reduction of ΔEpi during the CPT was associated with a higher AMSa in the placebo group (n=19, r = -0.58, P = 0.010). Removing one of the 19 subjects (who had the largest decrease of 1025 ng/ml during C) from these data decreased the probability of significance to 0.10 for the remaining 18 subjects, making this finding questionable.

The pain estimates demonstrate approximately the same mean values for each group, however, in the 9 common subjects the mean pain was greater during C than F, but this difference was not noted in the total group means and the ANOVA between the groups when all subjects were included. The paired-t analyses demonstrated that the pain was lower during the P than C trials. We anticipated that subjects who scored pain higher during the CPT might also tend to score their AMS higher, in that both are subjective ratings of discomfort. The results in Table 4-appendix show this to be the case for men, approaching significance (r = 0.42, P = 0.08), but the reverse trend (nearly significant) is noted in F (r= -0.40). The other three groups showed no relationship, similar to the result when all subjects were combined (table on previous page).

The ΔHR was largest in the men (Table 4-appendix) and smallest in L, but these means were not significantly different. The only significance noted was between C and P for the 9 common subjects, but the mean difference (5 bpm higher in P) was too small to be physiologically meaningful and was not supported by a paired-t analyses for all 20 subjects taking part in both runs.

The ΔMBP results in Table 4-appendix support the generalization that the men have a greater blood pressure response to the CPT than women, as significant differences were seen or approached in all four comparisons with women's subgroups. The paired analyses shows a trend for a lower response in the pill than placebo runs and this lower response is correlated with AMSa, which was slightly higher in P.

In summary, the association between these five cold pressor responses, presumably all indicative of an acute sympathetic response, are tenuous at best during our CPT, with the possible exception of ΔHR and ΔMBP. These would be most likely to agree because they are both components of the generalized cardiovascular component of the CPT response. The relationships between AMSa and the magnitude of these variables, indicative of a sympathetic response to localized pain, are not striking.

Ventilation

The total pulmonary ventilation ($\dot{V}_E$), measured at rest over a 5-min period during the control period and after hr 1, 6 and during the last hr at altitude, are given in Tables 5A, B and C-appendix for the men, menstrual cycle women and OCP subject groups, respectively. The relevant comparison is between $\dot{V}_E$ at C12 and at altitude to obtain the response to altitude by the five groups. In this way the functional ventilatory response to altitude can be compared. The response to altitude was calculated as the percentage increase in the average of the altitude values from the value before altitude at C12.

Males: The 18 men had a mean resting $\dot{V}_E$ of 8.0 L/min during control and a mean increase of 36% at altitude, based on the average of the three altitude measurements (Table 5A-appendix). Most of the change with altitude took place during the first measurement after one hr (+31%). The percentage increase was not correlated significantly with AMSa (n = 18, r= -0.10, P = 0.70).

Women during follicular and luteal menstrual cycle phases: The mean control resting $\dot{V}_E$ was the same during F and L (Table 5B-appendix), indicating that the higher endogenous progesterone during L did not alter baseline $\dot{V}_E$ during normoxia. The increase in $\dot{V}_E$ with altitude exposure was seen in both groups, but the mean increase was 9% greater in L, where $\dot{V}_E$ was about 1.0 L/min greater at A1 and A6 (paired-t values of 0.037 and 0.058, respectively). Although this higher overall percentage $\dot{V}_E$ response during L was seen in 15 of the 19 women, it was not significant (P = 0.27) as noted in the table below.

Statistical comparison of Δ%VE between men and women's subgroups.

	Group Total			9 Common Paired-t \ PROB \ ANOVA Group				All-paired			Δ%VE vs. AMSa		
	n	Mean	SD	Foll	Lut	C	Pill	n	Mean	SD	n	r	P
Men	18	36	25	0.12	0.63	**0.049**	0.06				18	-0.10	0.70
Foll	21	23	27		0.27	0.93	0.98	19	21	28	21	0.00	1.00
								P=0.15					
Lut	19	32	26	0.13		0.19	0.19	19	32	26	19	0.28	0.25
C (plac)	19	23	12	0.61	**0.031**		0.88	19	23	12	19	0.07	0.79
								P=0.68					
Pill	21	22	20	0.6	0.19	0.91		19	21	20	21	0.28	0.22
										All	**98**	**0.06**	**0.57**

These observations show that during L the increase in $\dot{V}_E$ at altitude is higher than in F, but this difference was not sustained during the 12-hr exposure. The increase in $\dot{V}_E$ as a response to altitude computed from all 40 runs from Table 5B-appendix was also not

significantly correlated with AMSa (r = 0.07, P = 0.65), similar to the observation in the men. This indicates that there was no attenuation of the AMS symptoms by the higher $\dot{V}_E$ in L. These analyses make it possible to answer the second hypothesis:

Hypothesis 2. Ventilation is greater at high altitude during the luteal phase of the menstrual cycle, and results in less severe symptoms of AMS compared with the follicular phase. Although $\dot{V}_E$ was higher in L than F and the AMSa was lower, neither of these differences approached statistical significance. However, the association implied in the hypothesis must clearly be rejected because the correlation between $\Delta\dot{V}_E$ and AMSa was positive for L (r = 0.28), although not significant, clearly in opposition to the hypothesis.

Women on oral contraceptives: The values in Table 5C-appendix demonstrate that baseline $\dot{V}_E$ values and those at altitude were very similar to those in Table 5B appendix, indicating that women on OCPs have about the same $\dot{V}_E$ and percentage increase at altitude as women not taking them. The differences between C and P, ranging from 0.3 to 1.1 L/min, did not approach significance until the last hr (Table 5C-appendix) in the paired measurements. The higher progestin levels in P may be responsible for this trend. In general, it is clear from the table on the previous page that the overall ventilatory response ($\Delta\%\dot{V}_E$) to altitude is greatest for L and men (34%) and lower and about the same for the other three groups (23%). It is now possible to answer the 7th hypothesis:

Hypothesis 7. Ventilation is greater at high altitude when women are taking oral contraceptives and results in less severe symptoms of AMS compared to when they are not taking oral contraceptives. The ventilation at altitude was smaller, on the average, for women on OCPs and their average AMSa was higher, clearly showing that this hypothesis must be rejected.

It is often presumed that greater ventilation during altitude hypoxia is associated with individuals who are tolerant to AMS. Although a negative correlation is observed between the mean AMSa in the groups in the table on page 21 and $\Delta\%\dot{V}_E$ in the table on the previous page (n = 5, r = -0.64, P = 0.25), this negative relationship is not seen when we consider all 98 comparisons in the table on the previous page (r = 0.06). Thus, this study does not support the common presumption of greater $\dot{V}_E$ being beneficial for reducing AMS.

Hypoxic Ventilatory Response (HVR) Test on Control Day

This test involves the gradual reduction of inspired O_2 over a period of 5 to 8 min until the SpO_2, measured by finger pulse oximetry, falls to 75%. As SpO_2 decreases, the ventilation

usually increases, depending on the hypoxic sensitivity. This is a "poikilocapnic" test, as alveolar PCO_2 ($P_{ET}CO_2$) is allowed to decrease with the increasing ventilation. The response is quantified by the slope value, calculated as the change in $\dot{V}_E$ (L/min) divided by percent reduction of SpO_2. This slope is typically negative and it is reported as a positive value so that the directional change corresponds directly with a change in hypoxic responsiveness. These slope values (usually about 0.2 L/min/%), obtained from the average of two response tests repeated after a 5-10 min period of normal breathing, are shown on the following table for the groups. Thirteen percent of the tests were not obtained because of technical difficulties in the data conversion process.

Statistical comparision of poikilocapnic HVR between men and women's subgroups.

	Group Total			5 Common Paired-t \ PROB \ Group ANOVA				All-paired			HVR slope vs. AMSa		
	n	Mean	SD	Foll	Lut	C	Pill	n	Mean	SD	n	r	P
Men	15	0.22	0.20	0.99	0.62	0.17	0.31				15	-0.28	0.32
Foll	18	0.22	0.17		0.56	0.12	0.23	15	0.23	0.18	18	-0.01	0.97
								P=0.24					
Lut	16	0.19	0.16	0.36		0.31	0.64	15	0.18	0.16	16	-0.45	0.08
C (plac)	16	0.13	0.17	0.17	0.35		0.36	16	0.13	0.17	16	-0.01	0.97
								P=0.20					
Pill	21	0.17	0.10	0.24	0.11	**0.048**		16	0.18	0.10	21	0.22	0.37
										All	**86**	**-0.12**	**0.25**

The ANOVA comparisons indicated that there were no significant differences between groups in this response test. The largest difference was noted between F vs. C (P = 0.12). In the five women who completed all four runs, there was a significantly lower response noted in their placebo tests as compared with their pill tests, however in all 16 women who completed both of these runs the paired comparison indicated a non-significant difference (P = 0.20). In terms of this response test predicting AMS tolerance (a high HVR response is thought to be a deterrent to AMS), only in L was this close to being significantly negative (P = 0.08). Considering all of the tests (n = 86), the r-value was only –0.12 (P = 0.25). This indicates that the HVR test is a slightly better predictor of AMS than the actual ventilation response to altitude, analyzed above, but is still not statistically supported. The comparison between $\Delta\%\dot{V}_E$ and the HVR slope (n = 86, r = 0.19, P = 0.08) indicates that the HVR test is positively, but insignificantly, related to the sustained increase in ventilation when subjects are exposed to altitude. This is not surprising, as secondary adjustments pertaining to acid-base changes

and fluid-regulating hormones come into play during the prolonged exposure and pulmonary and circulatory changes are more stable than during the short HVR test.

Isocapnic HVR tests were also given on the control day to all subjects. For this test, given after the two poikilocapnic HVR tests, the $P_{ET}CO_2$ was prevented from falling by adding a small amount of CO_2 to the inspired hypoxic gas mixture during the test. The increase in ventilation is therefore presumed to be solely induced by hypoxia because it is not attenuated by the normal concomitant hypocapnia that accompanies the normal increase in ventilation to hypoxia. The argument in its favor is that it is a true hypoxic response test, however it is not "physiological" in that stable CO_2 during an increase in ventilation is not encountered at true altitude. Because of technical problems in the data collection and software storage and analyses from these test recordings, 25% of these data were unacceptable. The results of the 72 tests that were satisfactory gave a mean slope value of 0.23. This is significantly greater, as expected, than the 0.19 value obtained for the poikilocapnic HVR slopes in these same subjects. The two HVR tests were significantly related between subjects ($r = 0.50$, $P<0.001$). The correlation coefficient with AMSa was -0.14 ($P = 0.24$), very similar to that noted for the poikilocapnic test in the table above. Therefore it appears that the results for the two HVR tests are very similar and neither can be reliably utilized in predicting AMS.

3-breath N_2 and O_2 Ventilatory Response Tests

These tests were administered immediately after performing the resting ventilatory and blood gas measurements at C12, A1, A6 and A12 while the subjects were still on the mouthpiece. The detailed procedures are given in a recent publication (11). These tests involved the inspiration of 3 consecutive breaths of N_2 and then, after allowing a few minutes for the return of normal ventilation, 3 breaths of O_2 in such a way that the subject was unaware of when they would be given. The changes in arterial oxygenation caused by this perturbation cause the ventilation to be acutely altered to an extent presumed to reflect ventilatory chemosensitivity (12,13).

During the baseline measurements at C12, the N_2 inspiration caused a mean transient drop in the arterial O_2 saturation (SpO_2), measured by a finger pulse oximeter (Criticare, model 503), of 10%. The average rise with O_2 was only 3%, because the starting saturation was normal at about 96%. At altitude (A1, A6 and A12) these inspired gases were superimposed on a reduced SpO_2, which averaged 79% because the P_IO_2 was already reduced by the

prevailing hypobaric hypoxia, causing a further drop with N_2 of 17% (to 62%) and a rise with O_2 of 19% (to 98%).

The results of these acute hypoxic responses are given in Table 6-appendix. The values are all expressed in percent of the change in ventilation in reference to the one-min average measured just prior to the arrival of the test gas at the mouth. The N_2 test during C12 caused a mean transient peak increase in $\dot{V}_E$ of 29% for all groups. At altitude the mean increase was 42%, showing essentually no change over the three serial measurements, suggesting no obvious change in chemosensitivity to an acute drop in arterial O_2 over 11 hr at altitude. However, the average value of 42% at altitude was significantly higher than the value of 29% measured at C12, which is not surprising because the saturation drop (stimulus) was nearly twice as great at altitude. The O_2 test can be considered as a chemoreceptor "off" response, because it measures the degree of hypoxic ventilatory drive existing prior to receiving the O_2, which removes the drive and ventilation falls. Because this can reduce the $\dot{V}_E$ only to zero, this reduction measured as a percent change from baseline, can be less than the N_2 "on" response. This is evident in the results, as the O_2 values are about half as large as for those for N_2. Again, there was no significant change in values with the O_2 test with time at altitude from A1 to A12. The change was about three times greater at altitude than during C12, where the rise in saturation was only 3% and the hypoxic drive was minimally active at normal arterial O_2 levels.

The relationship of the acute change in ventilatory response between the N_2 and O_2 tests was determined by a linear least squares regression between responses for the N_2 and O_2 tests for all chamber runs; the means are shown in Table 6-appendix. If the N_2 and O_2 tests measure the same responsiveness, the r-value should be negative and close to 1.0. During C12 there was a significant, but not impressive relationship between these tests ($n = 96$, $r = -0.22$, $P = 0.032$). However, the r-values at A1, A6, A12 and the average altitude value (Aav) were all non-significant, with r-values ranging from –0.09 to –0.12 and P values from 0.26 to 0.42. These results suggest that these two tests do not measure the same hypoxic drive components. Apparently, the acute $\dot{V}_E$ increase triggered by sudden anoxia is different than the component of ventilatory drive acting during sustained altitude hypoxia, which is turned off by the acute increase in lung and blood O_2. This implies that the level of ventilation at stable hypoxia is set by factors in addition to ventilatory sensitivity, such as respiratory alkalosis, varying blood gases and autonomic stimulation. In support of this was the finding that the average N_2 response at altitude also did not show an expected direct relationship with the mean $\Delta\%\dot{V}_E$ shown in Tables 5A, B and C-appendix ($n = 97$, $r = -0.12$, $P = 0.23$). The

calculation of a percent change could alter the expected relationship between values from the N_2 test (positive) and the O_2 test (negative) because a higher baseline ventilation would attenuate the percentage increase due to a given stimulus from N_2 and potentiate the percent reduction for a given removal of the prevailing hypoxic stimulus by O_2. The positive relationship found between the O_2 test and $\Delta\%\dot{V}_E$ (n = 96, r = 0.08, P = 0.45) also shows that the acute response is not related to the change in ventilation resulting from sustained hypoxia.

Similar to the results presented earlier for $\Delta\%\dot{V}_E$, no relationship was found between the percent change in ventilation induced by the N_2 or O_2 tests and AMSa. When comparing the N_2 test results at altitude (Aav) with AMSa for all individuals where measurements were made (n = 97) the r-value was –0.04 (P = 0.72) and for O_2 the corresponding values were –0.02, P = 0.88. The values at C12 were also not related significantly. In considering each of the five subgroups, the luteal women were the only group in which an expected significant negative relationship was found between the average response to N_2 at altitude and AMSa (n =19, r = -0.50, P = 0.031). For the O_2 test, the results for placebo women approached statistical significance (n = 19, r = -0.45, P = 0.052), but the relationship was negative instead of positive, as postulated prior to making the measurements.

These results suggest that the acute ventilatory response tests did not serve to separate out subjects who had subsequent AMS, with the possible exception of the luteal women. Although a great amount of variability was exhibited in these response tests between subjects (e.g. the mean coefficient of variation between the 18 men in Table 6-appendix was 77% and within the same subjects it was 41%), the variations in these responses were not related to AMSa. Taken together with the $\Delta\%\dot{V}_E$ and HVR results above, it seems clear that the variations in AMS exhibited by our subjects were not significantly related to variations in ventilatory responsiveness as measured by acute tests or the prolonged response to stable hypoxia while at altitude.

Arterial Blood Gases

Blood gases were measured in samples obtained from a femoral artery after local anesthetic. The punctures were made during the last minute of resting ventilation, gas exchange and end tidal gas measurements. There is missing data because this procedure was technically challenging and under a time restraint and sometimes was not attempted due to residual bruising from prior experiments on the same subject. This occurred often during

placebo runs on subjects who took part in the experiment four times. The results are shown in Tables7A, B and C-appendix.

Males: The arterial blood pH increased significantly from C12 to hr 1 at altitude as $PaCO_2$ was reduced by the increased ventilation and PaO_2 dropped by about 30 mm Hg because of the altitude hypoxia. The PaO_2 measurements at C12 were too high because the laboratory calibrated the electrodes for values at altitude; therefore these are not tabulated. The normal PaO_2 for healthy adults at this elevation is approximately 75 mm Hg. From hr 1 to 12 at altitude, the mean pHa increased additionally by an average of 0.026 pH units as the $PaCO_2$ fell by another 5 mm Hg, although the total ventilation remained about the same as at hr 1 (Table 7A-appendix). The decrease in base excess calculated from these values (14) is 1.2 mEq/L over the 10 hr, indicating the increase in bicarbonate elimination by the kidneys over this time at altitude. The arterial PO_2 remained about the same over this time at altitude, as did the SaO_2, measured directly by hemoximeter, averaging 79% at A1 and A12. Table 7A-appendix also shows the change in the end-tidal (alveolar)-to-arterial PO_2 difference measured from the first to the 12th hour. The mean difference increased only 1.3 mm Hg ($P = 0.12$ vs. zero), indicating no appreciable decline in gas exchange efficiency. The development of diffusion impairment or right-to-left shunt would be expected to increase the PO_2 difference from A1 to A12. The arterial - alveolar PCO_2 difference showed a small significant reduction during the altitude exposure ($P = 0.038$), suggesting that if any change in ventilation/perfusion ($\dot{V}_A/\dot{Q}$) heterogeneity occurred over time at altitude, it would have been a beneficial reduction. There was no significant correlation between the change in either of these alveolar-arterial differences and AMSa ($P>0.47$ for both). The PaO_2 at A12 also did not show a significant relationship with AMSa ($r = -0.14$, $P = 0.57$), showing that the degree of hypoxemia was not significantly associated with AMS symptom development in the men.

Women during follicular and luteal menstrual cycle phases: The blood gas values on Table 7B-appendix are quite similar to those of the men, as are the changes from hr 1 to 12. One consistent finding was that the $PaCO_2$ was lower in all three measurements in the women than in the men (below). The differences between F and L noted at the bottom of Table 7B-appendix were small, although the pHa values were higher and $PaCO_2$ values lower at altitude in L, reflecting their higher effective ventilation. At C12 the $PaCO_2$ was significantly lower in L. In these women there was also no significant correlation between AMSa and PaO_2 at A12 ($P=0.20$), or between AMSa and the change in the alveolar–arterial differences during the time at altitude ($P>0.56$).

Appendix 3-D summarizes a poster presentation pertaining to the difference in ventilation between groups. The data supports the conclusion that women with normal menstrual cycles have higher ventilation than men, but their ventilatory response to altitude is about the same as men, considering the baseline ventilation and metabolic rate. Also shown, is that during L women have a higher effective ventilation than in F, but the latter still has a greater ventilation than men. These conclusions in appendix 3-D follow from an analysis of 17 pairs of measurements in women, interpolating $PaCO_2$ for two subjects in F based on $P_{ET}CO_2$, which then resulted in significant differences in $PaCO_2$ at A1 and A12. The probability levels in the summary table below are somewhat above 0.05 for the differences between L and F.

Statistical comparison of $PaCO_2$ at C12 and A12 between men and women's subgroups.

	Group Total			9 Common Paired-t \ PROB \ ANOVA Group				All-paired			$PaCO_2$ at C12 vs. AMS		
C12	n	Mean	SD	Foll	Lut	C	Pill	n	Mean	SD	n	r	P
Men	17	38.7	2.9	0.06	**0.001**	**0.004**	**<0.001**				17	0.27	0.31
Foll	15	36.8	2.4		0.08	0.13	0.07	13	36.7	2.5	15	0.56	**0.030**
								P=0.016					
Lut	18	35.1	3.0			0.86	0.94	13	34.8	3.3	18	0.03	0.90
C (plac)	10	35.3	2.2				0.90	5	36.7	1.4	10	0.15	0.67
								P=0.24					
Pill	14	35.2	2.1					5	35.5	1.2	14	0.11	0.71
										All	**74**	**0.20**	**0.09**

A12											$PaCO_2$ at A12 vs. AMS		
Men	18	31.1	2.5	**0.047**	**<0.001**	0.05	**0.002**				18	-0.17	0.50
Foll	19	29.2	3.0		0.14	0.95	0.23	16	28.8	3.0	19	-0.02	0.93
								P=0.26					
Lut	18	27.8	2.6			0.18	0.83	16	27.7	2.7	18	-0.02	0.95
C (plac)	12	29.1	2.6				0.29	9	29.6	2.3	12	0.07	0.84
								P=0.26					
Pill	17	28.0	2.9					9	28.8	2.6	17	-0.24	0.36
										All	**84**	**-0.07**	**0.53**

Women on oral contraceptives: These blood gas results are shown in Table 7C-appendix and the means are generally similar to those for the menstrual cycle women and the men. Because ventilation tended to be higher in P, the pHa was somewhat higher and $PaCO_2$ lower in P for all three measurements. The alveolar-arterial differences were quite similar to those in the men and in L and F.

Differences between groups and AMSa: In the table above, the group comparisons are shown in the usual way for $PaCO_2$ at C12 and A12. Insufficient pairs of data from the nine

common subjects were available to make statistical tests valid in those subjects. A comparison of $PaCO_2$ is a clear reflection of any changes in effective ventilation relative to CO_2 output resulting from altitude. The latter reflects metabolic rate and utilizing $PaCO_2$ eliminates variations in anatomical and alveolar deadspace, which may arise because of changes in breathing pattern or $\dot{V}_A/\dot{Q}$ heterogeneity. The second hypothesis must be reconsidered:

Hypothesis 2. Ventilation is greater at high altitude during the luteal phase of the menstrual cycle, and results in less severe symptoms of AMS compared with the follicular phase. There appears to be a statistical basis for accepting the statement that ventilation is higher in L than in F, based on $PaCO_2$. However, as shown in the table on the previous page, this greater ventilation was not significantly correlated with a lower AMSa.

The table on the previous page demonstrates that women have greater ventilation than men at the ambient P_B of Albuquerque and at an altitude of 16,000 ft because the $PaCO_2$ of men is higher at C12 and at A12 than in the four women's groups. These mean differences are very close to or exceed the probability levels required for significance in all comparisons. In order to determine whether the blood gas values were associated with AMS, correlation coefficients including all experiments with complete data were calculated between AMSa and the following measurements. The following results and conclusions can be drawn:

- $PaCO_2$ at C12: n = 74, r = 0.20, p = 0.09. Although not significant, this suggests that lower ventilation before altitude may be associated with subsequent AMS.
- $PaCO_2$ at A12: n = 84, r = -0.07, P = 0.53. A greater ventilation at altitude is not beneficial in preventing AMS.
- $PaCO_2$ at A12 minus $PaCO_2$ at C12: n = 73, r = -0.30, P = 0.010. Lowering $PaCO_2$ by increasing ventilation or reducing metabolic rate during the stay at altitude is associated with an increase in AMS severity, which is opposite to the presumed change prior to this study.
- PaO_2 at A12: n = 84, r = -0.20, P = 0.07. Hypoxemia tends to be associated with an increase in AMS symptoms, although the difference between sick and nonsick subjects was less than 2 mm Hg, as discussed on the following page in relation to $\dot{V}_A/\dot{Q}$.
- ΔPCO_2 (A12-A1): n = 78, r = -0.07, P = 0.55. The arterial-alveolar PCO_2 difference was reduced from hr 1 to hr 12 by only 0.4 mm Hg, which corresponds to a trivial reduction in $\dot{V}_A/\dot{Q}$ heterogeneity. This small change was not beneficial in reducing AMS.
- ΔPO_2 (A12-A1): n = 78, r = 0.08, P = 0.46. An increase in AMS severity is not associated with a widening of the alveolar-arterial PO_2 difference between lungs and blood. The mean increase of 1.9 mm Hg could be attributed to a progressive right-to-left shunt or diffusion

impairment (because increasing $\dot{V}_A/\dot{Q}$ heterogeneity was not supported by ΔPCO_2), but these processes, if they occur, are not related to AMS severity.

Ventilation/perfusion ($\dot{V}_A/\dot{Q}$) Heterogeneity and AMS

In an effort to provide a more comprehensive and sophisticated description of the relationship between $\dot{V}_A/\dot{Q}$ changes and AMS, we applied a model (15) to the measured pulmonary gas exchange input values in sick and nonsick subjects. Although this model was applied to each subject individually with inconsistent findings, the application of it to mean data of sick and nonsick groups is somewhat instructive.

We ranked all 99 subject runs on the 51 subjects by AMSa score (highest to lowest). Then we arbitrarily selected the runs for the first 13 individuals (upper quartile of subjects) that appeared at the top of the list. These were the "sick" subjects, made up by four men and nine women (mean AMSa = 7.9, SE = 0.3). This was repeated from the bottom of the list to determine the "nonsick" subjects, made up of seven men and six women (mean AMSa = 1.0, SE = 0.1). The table on the following page lists the mean values obtained for these two groups of subjects. The first 11 variables are input data for the model. Cardiac output (CO) was calculated as 3.5 X body surface area (m^2), as computed from height and weight by the DuBois formula. This was the value assumed at C12 and was adjusted by the same percentage for A1 and A12 as the percentage change in HR, thereby assuming that stroke volume does not change during the first 12 hr at altitude. We then applied the model to determine whether any changes occurring over time at altitude might indicate pulmonary gas exchange impairment, more specifically, $\dot{V}_A/\dot{Q}$ heterogeneity.

The output of the model is the standard deviation of the log-normal $\dot{V}_A/\dot{Q}$ distribution. In this application of the model it is assumed that there is no right-to-left shunt and no diffusion impairment. In the absence of large differences in other input variables, the degree of $\dot{V}_A/\dot{Q}$ heterogeneity can be roughly approximated as being proportional to the sum of alveolar-to-arterial PO_2 and PCO_2 differences. The model serves to obtain an exact numerical value on $\dot{V}_A/\dot{Q}$ distribution, regardless of the input variations. The SDLn$\dot{V}_A/\dot{Q}$ values can range from zero, in perfect lungs, to a mean value of 0.6 in healthy lungs, to 2.0 or more in patients with chronic obstructive lung disease. The table above shows that SDLn$\dot{V}_A/\dot{Q}$ increased by 0.13 in the sick subjects and 0.06 in the nonsick during the time in the chamber when AMS developed. Because all values remain in the range for healthy individuals at this level of hypoxia, and the changes are so small, it is extremely unlikely that AMS can be attributed to a deterioration of

Measurement	SICK (A1)	SICK (A12)	NONSICK (A1)	NONSICK(A12)
Hb (g%)	14.2	14.4	14.8	14.7
pHa	7.440	7.473	7.454	7.476
PaO_2 (mm Hg)	43.3	42.6	44.5	44.5
$PaCO_2$ (mm Hg)	33.6	28.4	33.1	30
$\dot{V}CO_2$ (ml/min)	220	190	226	229
$\dot{V}O_2$ (ml/min)	253	249	266	285
$P_{ET}CO_2$ (mm Hg)	31.0	27.1	32.2	30.0
CO (L/min)	7.94	8.70	7.82	8.17
F_IO_2	0.2082	0.2091	0.2095	0.2087
F_ICO_2	0.0019	0.0019	0.0018	0.0010
P_B (mm Hg)	426	427	426	428
SaO_2 (%)	79.1	78.7	80.9	80.2
$P_{ET}O_2$ (mm Hg)	46.3	48.0	47.0	48.2
$\dot{V}_E$ (L/min)	9.20	9.54	9.29	10.06
$\dot{V}a$ (L/min)	5.78	5.93	6.02	6.68
(A-a)PO_2 (mm Hg)	3.0	5.4	2.5	3.7
(a-A)PCO_2 (mm Hg)	2.6	1.3	0.9	0
$\dot{V}A/\dot{Q}$ (LnSD)	0.47	0.60	0.41	0.47
BE (mEq/L)	-1.1	-2.0	-0.5	-0.8

pulmonary gas exchange. There is no evidence of alveolar hypoventilation in the sick group from A1 to A12, because the effective ventilation ($\dot{V}a$ = total ventilation minus physiological deadspace) actually increased slightly in both groups. The PCO_2 difference decreased in both groups, suggesting no decline in $\dot{V}_A/\dot{Q}$ inequality, but there was an increase in the PO_2 difference of 2.4 mm Hg in the sick group and 1.2 mm Hg in the nonsick. A very small diffusion impairment, due to edema in the lungs, could account for this equally as well as our modeled small increase in SDLn$\dot{V}_A/\dot{Q}$. However, if this small diffusion impairment were incorporated into the model then the $\dot{V}_A/\dot{Q}$ distributions would show no reduction or a small improvement.

The values for base excess (BE) in the table above indicate a slightly greater reduction in the sick subjects during the time in the chamber, showing a greater decrease in bicarbonate than the nonsick group. This means that the renal excretion of bicarbonate was slightly

greater in the sick subjects. The pHa values for the two groups were quite similar at A12, although the sick subjects showed a greater rise with time at altitude and a greater decline in $PaCO_2$. This indicates that the degree of respiratory alkalosis was slightly greater for the sick subjects, but was well compensated because the BE showed little change. This greater alkalosis may have been related to the slightly greater potassium excretion in the sick subjects, as discussed subsequently under fluid balance.

In summary, deterioration of gas exchange in the sick group was trivially larger than in the nonsick group and it is inconsequential whether this small deterioration is attributed to an increase in diffusion impairment, right-to-left shunt or $\dot{V}_A/\dot{Q}$ heterogeneity.

Spirometry and Breathing Frequency

Spirometry measurements were obtained serially in order to determine whether altitude exposure was associated with any changes in pulmonary mechanics. Venous congestion, edema in alveoli or lung parenchyma could all contribute to reduced voluntary maximal expired airflow velocities. Previous findings in short term studies are equivocal, however, impairments noted to be associated with AMS have been reported from studies where subjects were exposed to altitude for many days (16). Measurements were made with an electronic spirometer (Vitalograph, model Alpha). At each time the subject performed a slow exhalation after a slow inspiration to measure vital capacity (VC) three times and the largest was recorded. Then followed three maximal forced exhalations after a slow and maximal inspiration. Of these three successive maneuvers, the one having the highest peak flow was recorded. Also recorded were the breathing frequency (f), measured during the 5-min period when resting ventilation was recorded, the vital capacity recorded during the peak forced maneuver (FVC), the peak flow (PF), the forced expired volume in one second (FEV1) and the flow rate at half of vital capacity (mid-maximal expiratory flow rate-MMEF). The latter is less sensitive to variations in voluntary effort than FEV1.

The data in the table on the next page were compared in relation to the control values at C12, the change from A1 to A12 and to AMSa. The subjects are the same as those for whom data is shown in the table on the previous page.

It is apparent that the sick group always had a higher breathing frequency (f), measured during steady state breathing. The differences were significant at A1 and A12. This accounts for the slightly greater anatomical plus alveolar deadspace ($1-\dot{V}a/\dot{V}_E$) of 0.38 in the

sick subjects compared to the nonsick (0.34) noted in the $\dot{V}_A/\dot{Q}$ table on page 38, but this was not large enough to cause a reduction in effective ventilation (Va) with altitude.

Meas.	Sick (C12)	Sick (A1)	Sick (A12)	Non (C12)	Non (A1)	Non (A12)
f (per min)	15.9	16.8&	18.6&	12.3	12.9	13.2
VC (L)	3.96	3.81	3.55#$	4.58	4.53	4.51
FVC (L)	3.88	3.85	3.61#$	4.46	4.47	4.40
FEV1 (L/s)	3.27	3.37	3.13#$	3.85	3.94*	3.92
PF (L/s)	7.02	8.05*	7.52	8.53	9.85*	10.17
MMEF (L/s)	3.45	3.86*	3.68	4.26	4.82*	4.77

*: $P<0.05$ for A1 vs. corresponding C12

#: $P<0.05$ for A12 vs. corresponding A1

&: $P<0.05$ vs. nonsick

$: $P<0.10$ between sick and nonsick in change from A1 to A12

In both groups the peak flow (PF) and maximal mid-expiratory flow (MMEF) increased significantly by 14% at A1 as compared to C12, which is almost exactly the amount predicted from the reduction in air density. The forced expiratory volume in one second (FEV1) increased by a smaller percent, but still significantly in the nonsick group. For FEV1, the change is less because most of the volume has been expelled by this time and density is not the factor it is during the initial part of the exhalation. The unforced and forced vital capacity (VC, FVC) and FEV1 declined from A1 to A12 in the sick subjects, but not in the others and the difference between groups bordered on significance. Very small reductions in VC have been previously reported upon acute reductions in P_B, but clear associations with AMS have not been reported in acute experiments.

One can speculate that sub-clinical edema in the lung parenchyma or congestion of pulmonary blood vessels led to this 250 ml reduction in VC by increasing the residual volume. On the other hand, these values may have been reduced because the sick subjects were not capable or willing to exert the effort required to forcefully expel the last part of the exhalation, which requires considerable effort.

Heart Rate, Arterial Blood Pressure and Body Temperature

These measurements are shown in Tables 8A, B and C-appendix. The men showed a 38% increase in HR at altitude, most of which had already taken place in one hr. This reflects the increase in cardiac output necessitated by the hypoxia. Stroke volume is presumed not to change early at altitude. There was a small reduction in mean blood pressure (MBP) after one hr at altitude, which then recovered. The interesting finding was a significant 1.0 °F (0.6°C) increase in body temperature by the 12th hr at altitude, primarily taking place during the last 6 hr at altitude. The chamber temperature was maintained at levels requested by the subjects.

The menstrual cycle women demonstrated similar changes in HR and MBP to the men, with the HR at C12 being significantly higher in the luteal than in the follicular phase for the same women. The body temperature again increased from C12 to A12, but the change was less in both groups than in the men. The rise in L was only half that in F, resulting from the small, but significant drop between C12 and A1. As expected, the mean body temperature was higher in L than F at each measurement time. The difference averaged 0.6°F and was greatest at C12 and A1.

In the women taking OCPs, the values and changes in HR, MAP and body temperature were consistent with the menstrual cycle women, with no significant differences noted between placebo (C) and pill (P) series at altitude.

Our measurement of body temperature by oral thermometer can be criticized; however, the same digital thermometer was used in each of the serial measurements on each subject. Any imprecision of the device is partially compensated for by the large number of measurements. The overall increase in body temperature was highly significant when combining all the runs where measurements were made: C12 vs. A12: mean increase = +0.46°F, n = 82, $P<0.001$ and A1 vs. A12: mean increase = +0.44°F, n = 82, $P<0.001$. Diurnal variation can be ruled out for C12 vs. A12, as these measurements were made at approximately the same time of day. The entire rise in temperature took place during the second half of the altitude exposure, as the mean difference from A1 to A6 was –0.04°F. For all subjects, the correlation coefficient of the rise in temperature from C12 to A12 (average = 0.46, SE = 0.10) and AMSa was –0.34 (P = 0.001), indicating that the rise in temperature was significantly greater in those runs where the subjects were more tolerant to AMS.

Body temperature is determined by heat production and heat dissipation. Assuming the heat production was the same (because $\dot{V}O_2$ measured during C12 and A12 was similar) then the heat dissipation must have been less at A12. The most likely reason would be a reduction of skin and peripheral blood flow, which would reduce heat loss and increase body

temperature. This reasoning suggests that the redistribution of blood away from the peripheral circulation at altitude is greater in subjects more tolerant to altitude and that peripheral blood flow and vasodilation are greater in those subjects experiencing AMS. This may relate to a greater vagal tone in the sick subjects. In small mammals, it is well known that hypoxia will reduce body temperature, by reducing metabolic rate, thereby conserving oxygen, but these responses have not been noted in humans. However, this is apparently the first evidence that simulated altitude for 12 hr is capable of elevating temperature in humans and further research in this area is required.

Body Water

The results for total body water (TBW), estimated from the plasma enrichment of D_2O, and extracellular water (ECW), estimated from bromide enrichment after an oral dose, and intracellular water (by subtraction) are given in Tables 9A, B and C -appendix. The plasma samples were analyzed for NaBr and D_2O by a commercial laboratory (Metabolic Solutions, Nashua, NH). In each case they were provided with baseline samples and at least one, and in most cases two, samples taken 2 and 3 hr after dose administration. The value of the latter two samples that gave the highest plasma concentration (lowest TBW or ECW) was chosen, as this was presumed to be the one reflecting the best equilibration. In the majority of cases, this was the 3-hr sample. The percent change of each of these water compartments (Δ%) from the control day (C12) to the altitude day (A12) are shown. In 19% of the experiments, determination of compartments at A12 was not possible because nausea and vomiting by the subjects due to AMS prevented the oral administration, absorption or equilibration of the D_2O and NaBr. A few of the values and percent changes shown in these tables are out of the physiological range. It is possible that the absorption and mixing of the indicators was affected by altitude to result in these spurious values. Results from five experiments gave changes in TBW that were greater than 20% (more than twice the largest observed change in body weight) and were excluded from the computations of means in the tables (values marked as bold) and the following quantitative description. All of the other values were included, as there was no reason to exclude them based on known unusual experimental or analytical procedures.

The overall mean volumes of the water compartments agree well with normal values given in the literature for appropriate age and gender (6). From the mean values in Table 9A-appendix, the average TBW/body wt was 0.63 for men and the ECW/TBW and ICW/TBW

ratios were 0.36 and 0.64, respectively. The mean compartment volumes for women were within one liter of each other for women tested during each menstrual cycles (Table 9B-appendix) or while on OCPs (Table 9C-appendix). The mean values for the ratios above were 0.51, 0.39 and 0.61, respectively, for all women. The lower TBW/wt for women than men reflects their higher fat percentage of total body weight, as shown in Tables 1A, B and C-appendix. Fat has a much lower water content compared with most other body constituents.

The main reason to measure body water compartments in this study was to determine whether these absolute and relative changes from C12 to A12 would be associated with the development of AMS. For example, an increase in ECW is indicative of general tissue edema, which indicates fluid retention (17). This is often noted in association with AMS (18).

Men: From the values in Table 9A-appendix, it is apparent that TBW remained essentually unchanged, but ECW increased by 2.1L (P = 0.057) with the altitude exposure and ICW decreased by 1.8L (P = 0.050). The percent change in ECW correlated significantly with AMSa (n = 17, r = +0.51, P = 0.035), but TBW and ICW did not (r = +0.36, P = 0.16 and r=0.24, P = 0.36, respectively), as shown on the following page. The average AMSa for the 10 men who showed an increase in ECW at altitude was 5.5 and the average of the 7 who had a negative change was 1.4 (P<0.001).

Women during follicular and luteal menstrual cycle phases: In the follicular phase (F), the mean values show a trend similar to the men in that ECW increased by 0.7L (P = 0.037) and ICW decreased by 1.1L (not significant) in the 16 women in whom values were obtained. In the luteal (L) phase there were essentually no changes in the three compartments in 13 women. In the 12 pairs where data was complete for F and L, the difference in ECW and ICW changes with altitude were not significant. Considering all menstrual cycle women together, the correlation with AMSa was significant for ECW (r = +0.57, P < 0.001 and TBW (r = 0.59, P< 0.001), but not with ICW (r = -0.04).

Women on oral contraceptives: During the placebo or control (C) trials, the mean increase in ECW was 0.7L, which was not significant, and TBW and ICW remained virtually unchanged. During the pill trials there were no appreciable changes in water compartments. For the 12 pairs of runs for C and P where complete data was obtained, there was a significant difference in the percent change of TBW (P = 0.004), but not in ECW or ICW. For all 29 experiments the correlations with AMSa were positive, but not significant for ECW (r = +0.10), TBW (r = +0.23) and ICW (r = +0.13).

Men and Women: These data suggest that for men and women, there is a small increase in ECW and a reduction in ICW with altitude exposure and that TBW remains about

the same. No change in TBW is to be expected, since measured body weight did not change more during the chamber exposures than the normal variation expected with this dilution technique for TBW. Combining all data for men and women from the tables (n = 75), both the percent changes in ECW and TBW from control to altitude correlated positively and significantly with AMSa (r = +0.43 and +0.40, respectively, P < 0.001 for both), but ICW did not (r = -0.04). As shown in the summary table for ECW below, there were no clear significant differences in altitude-induced changes between the five subgroups, although the difference between men and the pill group is almost significant.

Statistical comparision of Δ%ECW between men and women's subgroups.

	Group Total			9 Common Paired-t \ PROB \ Group ANOVA				All-paired			Δ%ECW vs. AMSa		
	n	Mean	SD	Foll	Lut	C	Pill	n	Mean	SD	n	r	P
Men	17	11.0	22.2	0.90	0.60	0.51	0.06				17	0.51	**0.035**
Foll	16	10.2	17.7		0.65	0.53	**0.041**	12	11.3	20.2	16	0.40	0.13
								P=0.64					
Lut	13	5.9	31.3			0.97	0.41	12	6.7	32.5	13	-0.81	**0.001**
C (plac)	14	6.3	15.5				0.14	12	6.0	16.0	14	0.56	**0.037**
								P=0.41					
Pill	15	-1.4	11.5					12	0.5	11.6	15	0.12	0.66
										All	**75**	**0.43**	**<0.001**

Results for ECW were available on only 3 of the 9 women who did all experiments, so this paired analyses was omitted. The direct correlation between ECW and AMSa in the subgroups and the total sample suggests that altitude illness and an increase in ECW are associated. Only during L was the correlation negative, suggesting that here the altitude exposure resulted in a reduction in ECW, but results were only available on 13 of the 19 subjects. A compensatory decrease in ICW was not associated with AMS, as expected, but an increase in TBW was. The latter did not correspond quantitatively with measured changes in body weight. Furthermore, an unexpected significant correlation was found between ECW and TBW for all 75 runs (r = +0.53, P < 0.001). The latter observation supports the speculation that there may be an equilibration artifact associated with AMS, which in some way attenuates the absorption, mixing and equilibration of both indicators within the body. Gender, menstrual phase or progestin dose levels in oral contraceptives do not seem to be correlated with this possible artifact.

Plasma Volume

The plasma volume (PV) was measured with Evans blue dye. These values were obtained from zero-time extrapolation of a 3-hr decay curve (occasionally 2-hr) of dye injected at the same time of day on the control day and after 9 hr at altitude. Samples were taken at 10, 20, 30, 60, 120 and 180 minutes after injection of 12 mg of dye and PV determined according to the methods described by Linderkamp et al. (19) and Foldager and Blomqvist (20). Dye concentrations were determined with a Shimadzu, model UV-120-02 spectrophotometer. Because of variations in injection rate and early mixing and to avoid biasing the decay curve towards the early points, the dye concentrations and exact times for 10, 20 and 30 min times were averaged to obtain a single point to be used along with the values at 60, 120 and 180 min. Since these subjects could not be studied fasting, as is usually stipulated for Evans blue, a pilot study was performed on the effects of eating prior to the study. In six subjects we found that eating increased the scatter of points on the decay curve, but only affected the estimated PV determinations by less than 0.3%.

Three other independent estimates of the change in PV (Δ%PV) from C12 to A12 were also available, which are based on the concentration or dilution of naturally occurring blood constituents. These are: 1) total plasma proteins ($\Delta\%PV_{TP}$) the hemoglobin-hematocrit ratio ($\Delta\%PV_{HH}$) and the plasma density ($\Delta\%PV_{PD}$). The equations for each are given below.

$$\Delta\%PV_{TP} = (TP_{C12} / TP_{A12} - 1) \times 100$$

$$\Delta\%PV_{HH} = (((Hb_{C12} / Hb_{A12}) \times (100 - Hct_{A12}) / (100 - Hct_{C12})) - 1) \times 100$$

$$\Delta\%PV_{PD} = (1 - ((PD_{A12}-PD_{C12}) / (PD_{A12}-1000.3)) \times -100$$

Plasma proteins were measured by dry chemistry, Hb by OSM3 (Radiometer), Hct by the microhematocrit method with no corrections for trapped plasma in calculation of PV and plasma density by density meter (DMA 58, Anton Paar, Graz, Austria) as previously described (21).

The plasma volumes with Evans blue and the changes with altitude exposure (Δ%PV) measured by each of the methods are given in Tables 10A, B and C-appendix. The mean plasma volume for all subjects was 50 ml/kg, 52 for men and 49 for the women, which is below the upper end of the ranges reported for healthy subjects from numerous other studies (6). A reduction in PV is usually observed after arrival at altitude (22), but the time-course and a clear

and direct association between the decrease and AMS have not been established, but a greater reduction in PV in altitude-tolerant subjects is often presumed.

A comparison of results from the four methods for altitude-induced changes in Δ%PV for all subjects combined, as well as those measurements in the "sick" and "nonsick" groups is summarized in the table below.

Statistical comparision of Δ%PV at altitude by 4 methods.

	All			Prob. of Sign. Diff. \\ r value				Δ%PV vs. AMSa			13 Sick		13 Nonsick	
Method	n	Mean	SD	E	TP	HH	PD	n	r	P	Mean	SD	Mean	SD
E	98	-6.0	12.2		0.30	0.29	0.20	98	0.15	0.15	-1.2	13.6	-12.4	12.3
TP	99	-3.7	5.7	0.06		0.60	0.37	99	-0.18	0.08	-4.6	5.5	-4.2	6.6
HH	99	-2.9	8.6	**0.017**	0.24		0.46	99	0.09	0.40	-2.7	7.3	-4.7	6.8
PD	93	-3.9	8.0	0.08	0.81	0.30		93	0.12	0.24	-2.8	9.0	-4.5	10.1

Underline: significantly different from zero

There is no method that is agreed upon as the "gold standard". The values in the table suggest that Evans blue measures something systematically different from the other methods because it gave the lowest mean r value (0.26) for Δ%PV compared with the others from regression equations calculated with each of the other three methods. Also, it gave a mean probability of the difference from each of the other three methods that was much less (0.05) than the mean for the other three methods. However, it was the only method that demonstrated a significant correlation between Δ%PV and Δ%ECW. A positive correlation would be expected, as PV is a component of ECW and they would be expected to change in parallel. The total protein method gave the smallest SD for Δ%PV, the hemoglobin-hematocrit (Hb-Hct) method gave the highest average r-value, indicating most appropriate directional changes and the plasma density method had the values most like the other three methods (highest average P-values for the difference). Thus, each method seems to have advantages, but comments below presume that the values from the Evans method are most valid.

Men: The average PV measured by Evans blue decreased by 3.0 % at altitude, showing a large scatter (SD = 12.2%), and was not significantly different from zero, but Δ%PV estimated by each of the other three estimates were significantly different from zero (P = 0.03 or less). The percentage change in PV was not significantly correlated with AMSa for any of the four methods, but approached significance with the total protein measurement (P = 0.06).

Women during follicular and luteal menstrual cycle phases: The average reduction in PV was about twice as large in these women as for the men and about equal in F and L. For F, Δ%PV was significantly different from zero by each of the four methods (P = 0.02 or less). Again, Δ%PV was not significantly correlated with AMSa for any of the four methods. For L, the results were similar, except that the smallest value of Δ%PV with the Hb-Hct method was not significantly less than zero. Combining all 40 experiments during menstrual cycles, the correlation coefficient with AMSa was significant for the PD method only (r = +0.32, P = 0.05).

Women on oral contraceptives: The average reduction in PV was less, but not significantly so, than that measured in women not on OCPs and quite similar to that of the men. During C, only the measurement with Evans was significantly different from zero and none of the four methods correlated significantly with AMSa. When on the pill (P), only the total protein method showed a significant change with altitude and none of the Δ%PV values correlated significantly with AMSa. Combining all 41 experiments, there was no correlation with AMSa for any of the methods, but the mean value for Δ%PV was significantly below zero for all methods except for Hb-Hct.

Men and Women: It is clear in considering all these data, that for both men and women there was a decrease in PV of approximately 4% with altitude exposure. In considering the Δ%PV calculated by all four methods, this change is not appreciably altered by gender, menstrual cycle phase, oral contraceptives or progestin levels. A significant association between AMSa and the reduction in PV was not found in the combined data with any, or the average, of the four PV methods. The table on the previous page for the 13 subjects who had the highest AMS score and the 13 with the lowest score shows that only the Evans method resulted in a significantly greater reduction in PV at altitude in nonsick subjects.

One reason for this poor association between AMS and the change in PV during altitude (where a smaller reduction, or even an increase in PV was expected in the sick subjects), may be the fact that some of the subjects with more severe AMS vomited towards the end of the chamber exposure. This would decrease their PV, making their measurements appear to be like those in altitude-tolerant subjects, where a greater decline in PV was expected.

Transcapillary Escape Rate (TCER)

TCER was estimated from the decay slope of the Evans Blue dye over 2-3 hr and the results are shown in Tables 10A, B and C-appendix. The values are expressed as the

percentage change in dye concentration per hr, which is representative of the rate of albumin loss from the vascular space. A greater TCER is indicated by a larger negative number.

During the control day (C12) the values for TCER ranged from -7.9 in the men (Table 10A-appendix) to –3.5 in the placebo group of women. This difference was significant (P=0.014), as was the difference between F and L (0.042, paired-t) and between C and P (P=0.007).

Of more interest in this study is the change in TCER with altitude exposure (shown as the "Diff" column in Tables10A, B and C-appendix). In men, the TCER decreased by an average of 1.3% at altitude from that measured on the control day. It also decreased at altitude during the follicular and pill runs, but increased in the other two subgroups of women. In the table below, these differences in TCER with altitude are summarized.

Comparision of ΔTCER (%/hr) between men and women's groups.

	Group Total			6 Common Paired-t \ **PROB**\ Group ANOVA				All-paired		
	n	Mean	SD	Foll	Lut	C	Pill	n	Mean	SD
Men	17	1.3	7.1	0.56	0.12	**0.016**	0.86			
Foll	20	2.5	6.0		**0.022**	**<0.001**	0.360	16	3.1	6.1
								P=0.048		
Lut	17	-2.6	7.1	0.07		0.59	0.09	16	-2.0	6.7
C (plac)	18	-3.7	4.2	0.17	0.59		0.00	16	-3.7	4.4
								P=<0.001		
Pill	19	0.9	4.9	0.59	**0.050**	**0.043**		16	2.0	4.5

These results, along with those in Tables10A, B and C-appendix, show that the change in TCER with altitude was significantly different between F and L and between C and P. They show that (a) in the menstrual cycle women in L, a lower control TCER was increased by altitude, whereas in F a greater control TCER was reduced by altitude and (b) in the women on OCPs, a lower TCER in the placebo run was increased by altitude, but the greater TCER in P was reduced by altitude. These changes do not correlate with progesterone/progestin levels and cannot be explained on that basis.

No significant correlations were found between the change in TCER from C12 to A12 and AMSa in any of the subgroups. For all 91 runs combined for which data were available the r-value was 0.10 (P = 0.35), making an association between AMS and ΔTCER unlikely.

The mean change in TCER at altitude for all 91 runs was -0.25%, which was not significantly different from zero (P = 0.71), indicating that altitude does not increase TCER, as suggested previously from other studies (23, 24). If altitude did increase TCER, a negative number significantly less than zero would have been noted.

Fluid Balance

Fluid balance is the difference between fluid intake and urine volume (flow rate) over the same time period. In order to explore these relationships in the present study and determine how fluid balance may be affected by fluid-regulating hormones during the development of AMS, the data for 13 sick and nonsick subjects were first separated and compared. Then, fluid balance and hormone values were analyzed by groups.

AMS, Fluid Retention and Related Hormones

In order to determine the relationship between these variables and AMS, a similar approach to that for gas exchange was applied. Thirteen subjects having the highest AMSa scores were chosen as the sick group and 13 with the lowest scores constituted the nonsick group. The latter were the same individuals utilized for the gas exchange comparison and 3 new subjects were substituted in the original sick group because of incomplete fluid data. The mean AMS score of the nonsick group remained at 1.0 (SE: 0.1) and the sick group now had a mean score of 7.62 (0.4) and was now made up of 6 men and 7 women.

Fig. 2 on the next page shows the average fluid intake, urine volume and the balance (in-out) for the two groups and the SE of the measurements at the noted times. C12 is the value over a 3-4 hr period on the late afternoon-early evening of the control day and A3, A6, A9 and A12 are the 3-hr intervals at altitude, ending at about the same time of day as the C12 measurements. As previously stated, at altitude the subjects were encouraged to maintain a fluid intake approximating the cumulative volume of the previous interval's urine flow, after beginning the chamber exposure with an extra intake volume of 0.5% of body weight (approx. 300 ml). Fig. 2 shows that the sick subjects had about the same intake during the first 3 hr at altitude and slightly reduced intakes from the nonsick thereafter (not significantly different at any time). Both groups had a significant reduction of intake near the end of the chamber stay relative to baseline. The urine volume decreased continuously with time at altitude in the sick subjects, but the decline was delayed in the nonsick subjects so that by 9 hr the urine flow in the sick subjects was significantly lower. The resulting fluid balance was not significantly different at any time. However, relative to each group's baseline over the 12 hr at altitude, the

sick group had a cumulative 360 ml lower intake and a 1,440 ml lower urine volume than the nonsick subjects. This resulted in a net positive balance over 12 hr that was 1,077 greater in the sick subjects. This clearly demonstrates fluid retention in AMS, primarily because of the reduced urine flow.

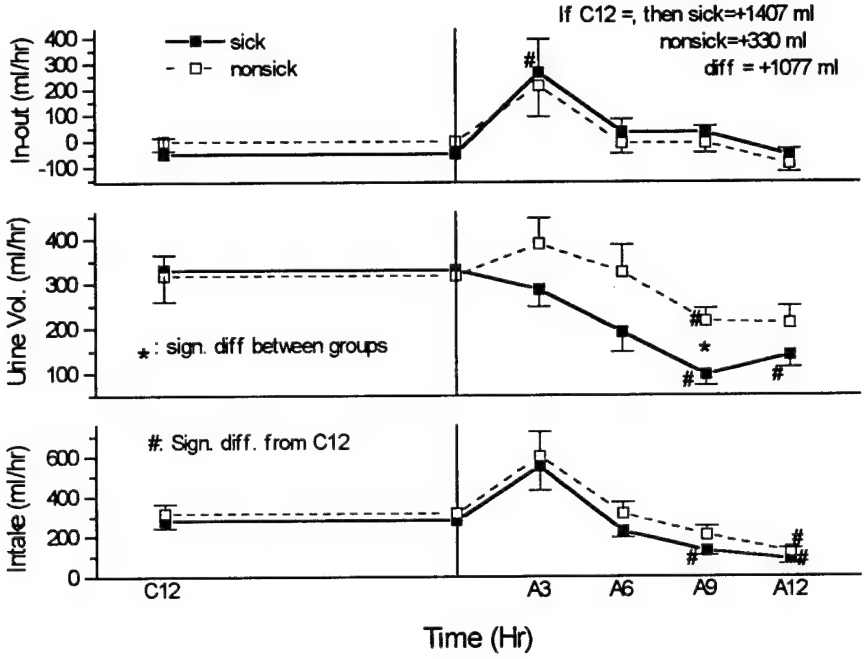


Fig. 2. Intake, urine volume and fluid balance in two groups.

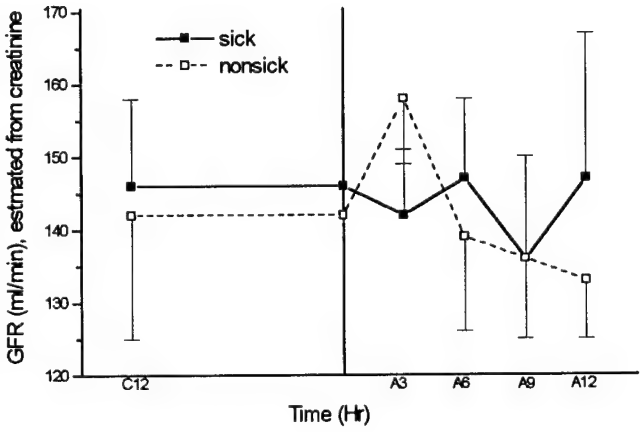


Fig. 3. GFR in two groups.

Fig. 3 on the previous page gives the values for glomerular filtration rate (GFR), as estimated from creatinine clearance. There were no significant differences between the groups and the changes with altitude were minimal.

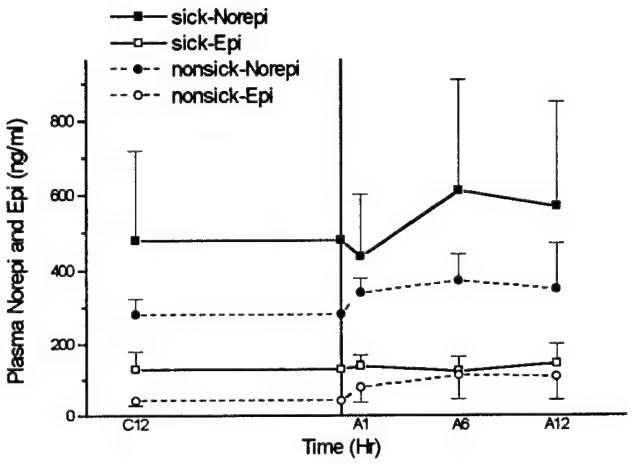


Fig. 4. Plasma Norepi and Epi in two groups.

Fig. 4 shows the plasma epinephrine (Epi) and norepinephrine (Norepi) levels during C12 and the three serial measurements at altitude. There were no significant changes with altitude in either group or significant differences between groups. The values for both hormones tend to be higher in the sick group and the variability for Norepi is greater in the sick group, but even combining all measurements there were no significant differences.

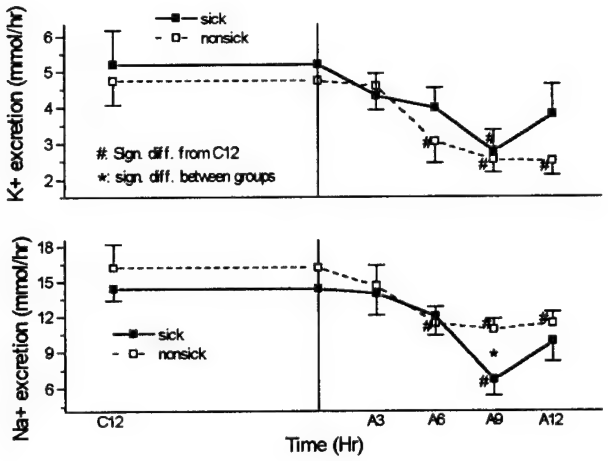


Fig. 5. Sodium and potassium excretion in two groups.

Fig. 5 demonstrates the potassium (K+) and sodium (Na+) excretion for the two groups. It shows that K+ excretion is reduced at altitude in both groups, slightly less in the sick subjects. The differences were not significant between groups at any time. However, the Na+ excretion was significantly reduced more in the sick group after 9 hr.

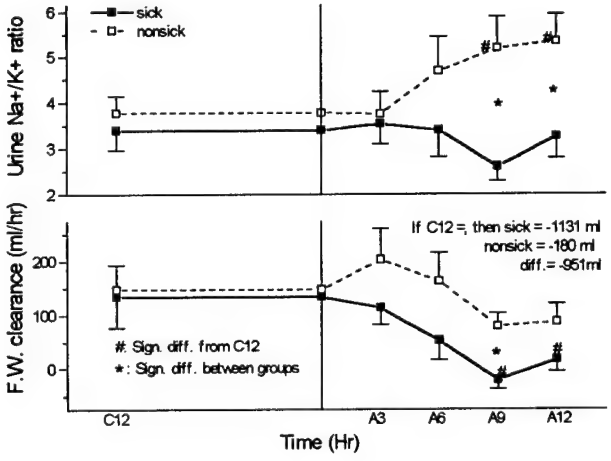


Fig. 6. Free water clearance and urine Na+/K+ ratio in two groups.

Fig. 6 shows free water, calculated as urine volume minus osmolar clearance. A water diuresis (dilution of the urine when eliminating excess intake) is characterized by positive

values for free water and when urine is being concentrated because of reduced intake or for other reasons, these values decrease and become negative. The responses of free water in the two groups is almost identical with urine volume, shown in Fig. 2 on page 50, indicating that the regulation of the osmolality of body fluids by the loops of Henle, distal tubules and collecting ducts differs between the two groups. The time course between groups is different in Fig. 6. The extra fluid taken in by both groups shortly after being taken to altitude is reflected more rapidly by an increase in free water clearance (at A3) in the nonsick group, but in the sick group the elimination of this extra load is impeded as their free water clearance immediately begins to decline. The cumulative reduction in free water clearance over 12 hr at altitude is nearly 1.0 L greater in the sick subjects, about the same as the reduction in urine volume. Such a response is usually associated with an elevation of ADH (page 55). Also shown in Fig. 6 is the ratio of urine Na+/K+, a somewhat arbitrary index, which was very clearly associated with AMS in our study. This index reflects the urine concentrating response of the sick subjects as their fluid-regulating mechanism is stimulated to conserve and retain fluid.

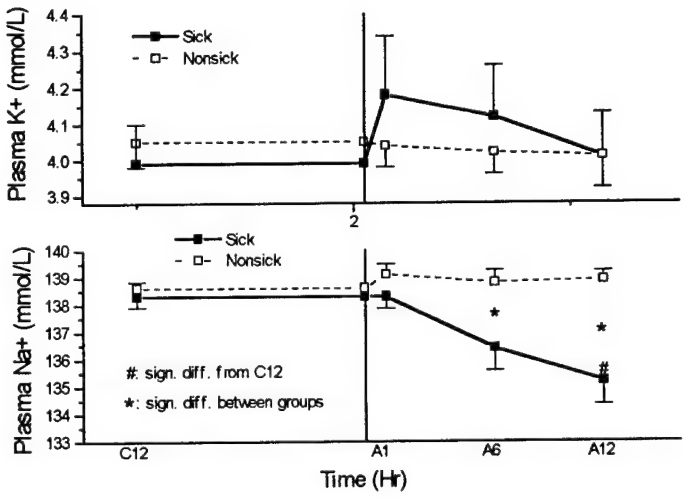


Fig. 7. Plasma Na+ and K+ in two groups.

Fig. 7 depicts the plasma concentrations K+ and Na+. Although there was an increase of K+ initially at altitude in the sick subjects, it was not significant compared with baseline or the nonsick subjects. Surprisingly, the Na+ fell in the sick subjects, however, even though their Na+ excretion fell more than in the nonsick (which would be expected to increase the plasma

levels), the retention of about 1.0 L of free water in the extracellular space (of about 15 L volume) would serve to dilute the plasma Na+ by approximately the extent shown.

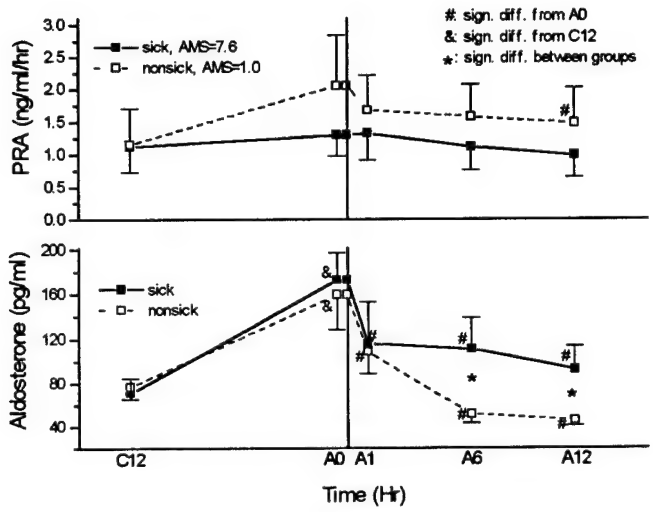


Fig. 8. Plasma aldosterone and renin activity in two groups.

In Fig. 8 are shown the expected higher ALDO levels in the sick subjects. The baseline (C12) values and the overnight changes are practically identical for the two groups. However, the time courses became significantly separated between 1 and 6 hr at altitude. The concentration fell in both groups during the first hour at altitude, but continued to fall in the nonsick to levels significantly below those for the sick subjects by 6 and 12 hr. The PRA was not significantly different between groups, although it tended to be lower in the sick group. This is unexpected because PRA and ALDO are usually directly related.

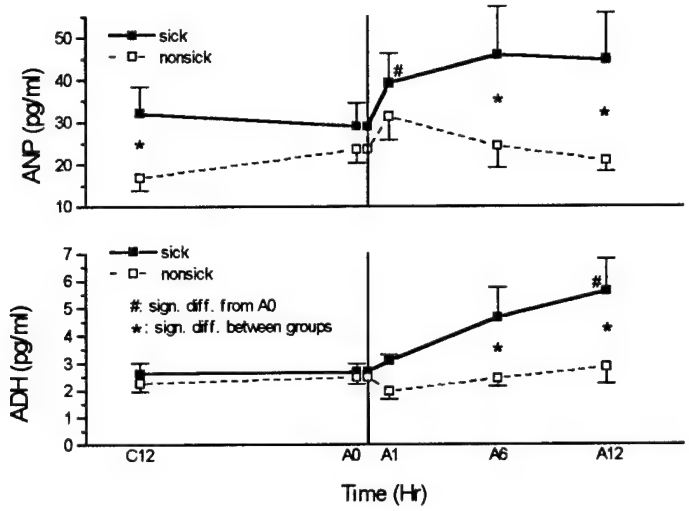


Fig. 9. Antidiuretic hormone (ADH) and atrial natriuretic peptide (ANP) in two groups.

Fig. 9 shows the plasma values for antidiuretic hormone (arginine vasopressin-ADH) and atrial natriuretic peptide (ANP). It shows that ADH was significantly elevated in the sick subjects after 6 and 12 hr at altitude and was probably elevated already after the first hr. This higher level of ADH by the sick subjects served to increase body fluid volume and reduce the urine flow, as noted previously. The ADH levels were not affected by altitude in the nonsick subjects and were about the same and unchanged in both groups at C12 and A0, showing that there was no overnight change between early evening of the control day and the next morning prior to entering the chamber. ANP, also shown in Fig. 9, demonstrated a response somewhat similar to ADH in that it rose significantly in the sick subjects at altitude. However, the baseline values were significantly higher in this group as well. We therefore considered this value at C12 as a possible predictor of AMS and calculated the r-value for the ANP concentration at C12 and AMSa. This was in the positive direction indicated by the 26 subjects ($r = 0.16$), but was not significant for all the runs ($n = 98$, $P = 0.12$).

The picture that emerges from the consideration of the 13 sick and the 13 nonsick subjects above is that ADH is released early in the AMS-prone subjects, perhaps by nausea precipitated early by the hypoxia, before true AMS symptoms are evident. This rise in ADH probably simulates both aldosterone and ANP release (25, 26, 27). The increased levels of ALDO and ADH both inhibit Na+ and water excretion as time progresses at altitude until subsequently fluid retention results in the symptoms of AMS after some hours. The role of

ANP, later during altitude exposure, is not clear because hypoxia has been shown to be influential in causing a dissociation between ANP and aldosterone levels and function (28, 29).

Urine Volume in Subgroups

Intake is controlled by thirst, considering the stipulations below and urine volume was recorded over five 3-hr intervals. It should be recalled that we attempted to have the subjects in a state of fluid balance on the control day and prior to arriving at the chamber for the altitude exposure. Then, just prior to the 3-hr collection interval on the control day and just before entering the chamber, the subjects were given a fluid overload by having them drink a volume equal to 0.5% of body weight to ensure an adequate urine flow. Thereafter, the subjects were asked to drink a minimum of fluid to replace their urine volume accumulated over the previous 3-hr interval. This meant that fluid intake was matched, at least approximately, to any diuresis or fluid retention that occurred as a response to altitude.

In order to estimate the general change of urine flow (ml/hr) occurring over time at altitude, we computed the percentage change in urine flow averaged for the last two collection intervals (A9 and A12) relative to the average urine flow on the control day (C12) and the urine flow at A3. The equation is shown below:

$$(((A9+A12)/2 - (C12+A3)/2)/(C12+A3)/2) \times 100$$

A decreased urine volume is typically expected in subjects experiencing AMS (supported by the sick and nonsick group results) and a diuresis is considered to be a beneficial response to acute altitude (30). The results for urine flow are shown in Tables 11A, B and C-appendix.

Men: All but 3 men showed a decline at altitude and the mean reduction in urine flow was 45%, as shown in Table 11A-appendix. The correlation between the change in urine flow and AMSa was in the direction expected, but not significant ($r = -0.18$).

Women during follicular and luteal menstrual cycle phases: About the same average decline in urine flow (37%) was seen in the menstrual cycle group of women as in the men, with no mean difference between L and F (Table 11B-appendix). The diuresis was not significantly correlated with AMSa in F ($r = -0.32$, $P = 0.16$), but it was in L ($r = -0.58$, $P = 0.009$). Combining all 40 subjects resulted in a significant r-value of -0.41 ($P = 0.008$) between the change in urine flow and AMSa.

Women on oral contraceptives: The mean percent decline in urine flow at altitude was the same in these two subgroups of women (Table 11C-appendix) and the same as in women not taking OCPs. The change in urine flow at altitude in C was better correlated with AMSa ($r = -0.44$, $P = 0.053$) than in P, where there was no clear relationship ($r = -0.07$). In all 41 of the OCP women, the correlation was apparent, but not significant ($r = -0.27$, $P = 0.08$).

Men and Women: The relationship between AMSa and urine flow in all 99 subjects combined was significant ($r = -0.27$, $P = 0.008$), thereby demonstrating that AMS is clearly associated with a reduced urine flow, as was clear in the comparison of the 13 sick and nonsick subjects above. However, a cause-and-effect relationship cannot be shown by these data. The large variability in these measurements indicates that additional factors are probably also significant as potential causes of AMS.

Fluid Balance in Subgroups

In Tables 12A, B and C-appendix are listed all intake, urine volume and calculated balance values obtained on all the subjects. Slight variations in mean urine flow, compared with Tables 11-appendix, are apparent because a few adjustments to individual values were made at A12 to make it possible to compute the balance. Also, the average was taken for one subject who completed two runs and data for fluid intake were not available for one subject.

The intakes were quite variable on all the subjects, and when combined with the variations in urine flow, resulted in very large variations in calculated balance. The balance value at C12 was determined over a 3 to 4-hr interval and it could be argued that a value of zero should have been assumed at C12 because the value may not have been representative of the subject's true baseline. However, it was utilized because it probably reflects each subject's balance at that time of day and makes the comparison with A12 more accurate. The C12 value was subtracted from the subsequent values for the 3-hr intervals at altitude. The mean values from Tables 12A, B and C-appendix demonstrate that the largest positive value occurred at A3 (78 ml/hr), indicating the extra fluid intake just before this interval or during the first hr in the chamber. The means were also positive during A6 (35 ml/hr) and A9 (69 ml/hr), but negative during A12 (-12 ml/hr). The cumulative net balance was calculated as follows:

$$4((A1-C12) +(A3-C12)+(A6-C12)+(A9-C12)+(a12-C12))$$

This gives the cumulative balance over 12 hr at altitude. This calculation ignores the

approximate 400 ml insensible water loss, estimated over 12 hr. The statistical comparison for total balance at altitude is shown in the table below for all the subgroups.

Statistical comparision of fluid balance (ml/12hr) between men and women's subgroups.

	Group Total			9 Common Group Paired-t \ PROB \ ANOVA				All-paired			ml/12hr vs. AMSa		
	n	Mean	SD	Foll	Lut	C	Pill	n	Mean	SD	n	r	P
Men	18	531	2459	0.27	0.74	0.58	0.73				18	0.23	0.36
Foll	21	1243	1495		0.06	**0.024**	0.05	19	1383	1429	21	0.37	0.10
								P=0.016					
Lut	19	307	1588	0.06		0.77	0.99	19	307	1588	19	0.74	**<0.001**
C (plac)	20	166	1441	0.06	0.55		0.78	19	136	1473	20	0.29	0.22
								P=0.74					
Pill	20	302	1542	0.22	0.71	0.86		19	318	1583	20	0.18	0.46
										All	**98**	**0.32**	**0.001**

The values ranged from 1,243 ml in the follicular women to 166 in the placebo group. Because of the large variation within groups only a few significant differences emerged. The value for follicular women was significantly larger than for the placebo group and the pill group by ANOVA (P = 0.051), and nearly significantly larger than in the luteal runs (also indicated by P = 0.06 for the 9 common women). However, the paired-t test between L and F gave a highly significant difference. There were no apparent differences between C and P by any of the three comparisons. In all five groups the net balance correlated positively with AMSa, but this was significant only in the L and when combining all subjects. The correlation was slightly superior to the negative r-value (-0.27) between urine volume and AMSa, noted on the previous page. The answer to the 3rd hypothesis is now apparent:

Hypothesis 3. Fluid retention in response to altitude is greater during the luteal phase of the menstrual cycle, but in those with high ventilatory response fluid retention does not result in AMS. The first part of the hypothesis must clearly be rejected based on the results in the table above. The answer to the second part of the hypothesis must also be rejected on statistical grounds. However, the earlier observation that the luteal women had the largest $\Delta\%\dot{V}_E$, the lowest average AMSa and a significant negative correlation between the acute N_2 ventilatory response test and AMSa, suggests that a greater ventilation in hypoxia may prevent fluid retention in this group. Thus, the second part of the hypothesis bears some merit and cannot be summarily rejected. The 8th hypothesis can also be answered:

Hypothesis 8. Fluid retention is reduced when women are taking oral contraceptives and results in less severe symptoms of AMS compared to when they are not taking oral contraceptives. This must be rejected on statistical grounds because the average AMSa was higher in women taking OCPs than in women not taking them, although the difference was not significant. The table on the previous page shows that fluid retention was similar when taking OCPs as in the luteal phase. Although there is statistical evidence in the table that fluid retention is lower for both C and P than during F, the hypothesis cannot be accepted as stated.

Fluid-regulating Hormones in Subgroups:

The results by subgroup for PRA and ALDO are given in Tables 13A, B and C-appendix and in Fig. 10. Those for ANP and ADH (arginine vasopressin) are in Tables 14A, B and C-appendix and Fig. 11 on the next page. Statistical summaries between altitude and C12 values and between F vs. L and C vs. P are given at the bottom of each of these tables.

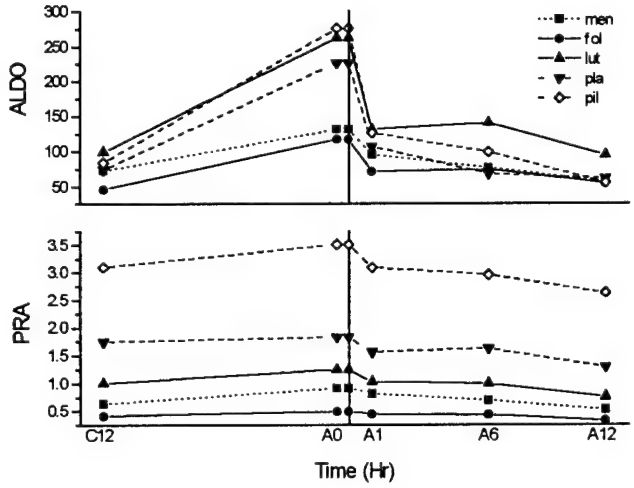


Fig. 10. Mean PRA and ALDO in five subgroups.

PRA shows the same time pattern in each group (Fig. 10), in rising overnight from C12 to A0 and then showing a small drop by A1 and a further downward trend by A12. The values were always significantly higher in L than in F. On OCPs the PRA was always higher than when not taking OCPs and the values were always higher when the progestin levels were elevated (pill phase) as compared to C. Because blood pressures were not different in these

four subgroups it suggests that both endogenous and exogenous progesterone may serve to elevate PRA. The time course for ALDO was about the same as for PRA in all groups, but the rise overnight and the fall after one hour of altitude were more pronounced than for PRA. Similar to PRA, the ALDO was significantly higher (approximately doubled) during all times in L as compared to F. There were no significant differences between P and C and both of these groups had values approximating those in L.

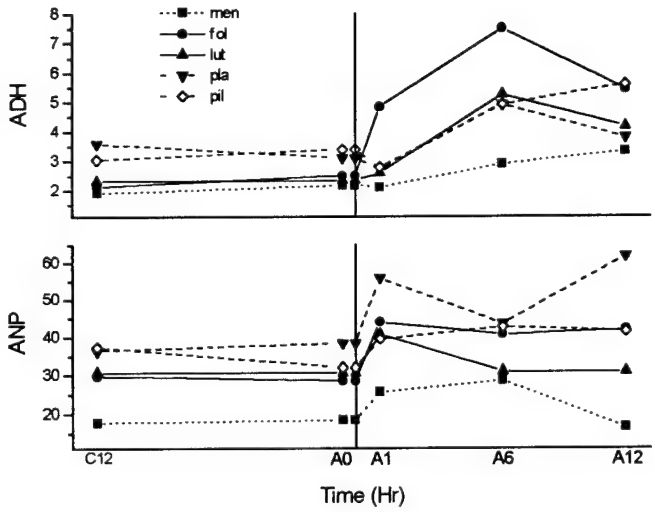


Fig. 11. Mean ANP and ADH in five groups.

For ANP (Fig. 11) there was little change overnight and then a small rise during the first hr at altitude, which was only significant in L. Thereafter the results were variable. The values were always lowest in the men and about the same in the four groups of women with no significant differences between F and L or between C and P. The ADH also did not show large changes overnight preceding the altitude exposures, although the small increase for the men was significant. At altitude the rise was greatest and highly significant for F and L by A6, being largest for F, where the fluid retention was the greatest. Differences between F and L and between C and P were not significant at altitude.

Previous comparisons of these hormones during cycle phases have reported higher PRA and ALDO levels in L and slightly higher ANP values than in F and no difference in ADH (31). Another study also demonstrated the differences in ALDO, but found no significant differences in ADH or PRA (32). A recent report has suggested that OCPs can lower PRA and ALDO, which is not what was observed here, and that ANP and ADH were little altered by

OCPs, as supported by our data (33). Undoubtedly, many of these findings pertaining to menstrual cycle differences and OCP effects will be variable because of each subject's individual differences in the cyclical changes in progesterone and estrogen at the time measurements are made. It seems clear from the present study that fluid retention is most likely to occur at altitude in the follicular phase, but this does not cause an increased incidence of AMS. The ALDO levels were doubled in L, but exposure to altitude did not cause an increase in AMS in this group.

Autonomic Nervous System

In order to determine whether the sympathetic and parasympathetic nervous system were affected by altitude and whether these responses were related to AMS, we considered the results of the plasma levels of epinephrine (Epi) and norepinephrine (Norepi) and heart rate variability (HRV).

Plasma Catecholamines

Plasma Norepi and Epi were measured in plasma from the first venous sample taken during the blood draws at C12, A1, A6 and A12. Prior to this blood draw from the indwelling catheter, the subjects rested with lights out with noise and activities minimized in the chamber. The analytical methods were described previously under cold pressor tests. The results (pg/ml) for both hormones are shown in Tables 15A, B and C-appendix, by subgroups as in the previous tables, and in Fig. 12 on the following page. Because both hormone levels, especially Epi, are related to stress and emotional responses, a large variation in measurements is to be expected in a study of this nature. Large fluctuations are attributable to the act of sampling and variations in AMS symptoms.

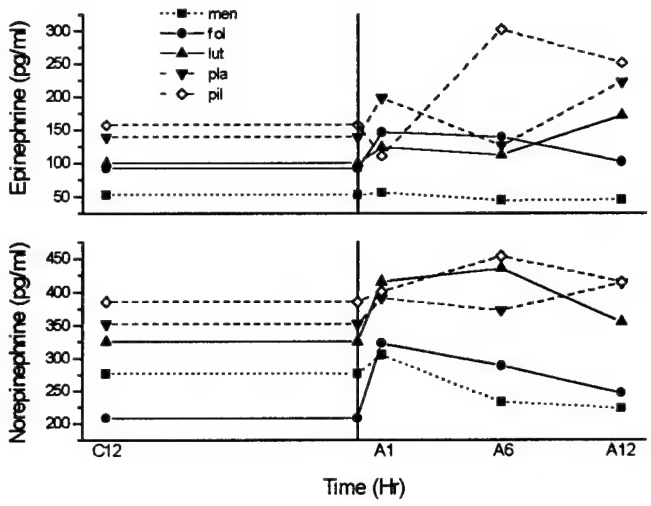


Fig. 12. Mean plasma Norepi and Epi in five groups.

In Fig. 12 the general pattern is that the catecholamines increase at A1, assuming that the values at C12 were still representative of levels the next morning at A0, and then either decline or remain elevated. In the men (Table 15A-appendix) both hormone levels increased slightly from C12 to A1 and then fell below the control baseline. However, none of the mean values were significantly different from the C12 values. The menstrual cycle women showed greater fluctuations than the men (Table 15B-appendix). In F the Norepi and Epi increased 57% from C12 to A1 and then declined, but still remained above baseline. The elevations in Norepi at A1 and A6 were significantly higher than control ($P<0.001$ and $P = 0.011$, respectively) and the Epi levels were also significantly elevated ($P = 0.08$ and $P = 0.050$, respectively). These trends were similar for Norepi during L, but less marked (26% increase) with lower significance levels, but changes in Epi were not significant. The Norepi levels were always higher in L than F, but the only significant difference was at A6. In the women taking oral contraceptives (Table 15C-appendix), the catecholamines were about the same in C and P and tended to not increase as much at A1, but rose to higher values at A6 and A12, the latter being significant for Epi in P at A6.

The mean values at C12 for each of the five groups were compared by ANOVA, but none of the differences were significant for Norepi or Epi. However, as stated above, the paired-t comparison between F and L and between C and P yielded some significant differences as shown at the bottom of Tables 15B and 15C-appendix. The Norepi was

significantly higher in L compared to F during C12 and A6, and for women on OCPs the Epi levels tended to be higher in P during A6.

The relationship between AMS and catecholamines levels during baseline and early altitude was tested by calculating the significance of the linear correlation coefficient (for all runs where data was available) between AMSa and the catecholamine levels at (a) C12, (b) at A1 and (c) the change in catecholamine levels from C12 and A1 (A1 minus C12 = Δ). The results are shown below:

AMSa vs. Norepi at C12: n=98, r = 0.12, P = 0.24 and vs. Epi: n = 93, r = 0.17, P = 0.09

AMSa vs. Norepi at A1: n = 98, r = 0.13, P = 0.19 and vs. Epi: n = 93, r = 0.24, P = **0.022**

AMSa vs. ΔNorepi: n = 98, r = -0.01, P = 0.92 and vs. ΔEpi: n = 90, r = -0.07, P = 0.52.

This suggests that subjects with a relatively high Epi and Norepi during baseline and after one hour of altitude exposure tend to be the ones more likely to experience greater subsequent AMS. In other words, a higher sympathetic tone before or early during altitude seems to be a negative factor for AMS tolerance.

Previous reports of catecholamine levels at altitude have shown inconsistent results, primarily attributed to the variations of time spent at altitude in laboratory and field studies and the confounding effects of other variables during the latter (34). In summary, the results from this study do not demonstrate marked differences in catecholamines between gender before and during altitude exposure. However, they show that during L the baseline Norepi is higher than in F and remains elevated during altitude exposure. In spite of the overall tendency for a positive relationship between early elevations of catecholamines and AMS, L had the lowest mean AMSa of the five subgroups.

Heart Rate Variability (HRV)

HRV was obtained from continuous analog recordings of the resting ECG during the time when pulmonary gas exchange was measured at C12, A1, A6 and A12. These recordings were 5 min in duration. Tachograms were created from digitized ECG records and then a frequency-domain analysis was performed. The frequency and amplitude (power) spectra of the oscillatory components were extracted by fast Fourier transform. The low frequency range (LF) was chosen at 0.04 - 0.15 Hz and the high frequency range was defined as 0.15 - 0.40 Hz as per consensus recommendation (35).

An example of an ECG tracing and it's analyses into LF and HF components is shown in Fig. 13 on the following page. We utilized the rationale presented by Malliani (36) to

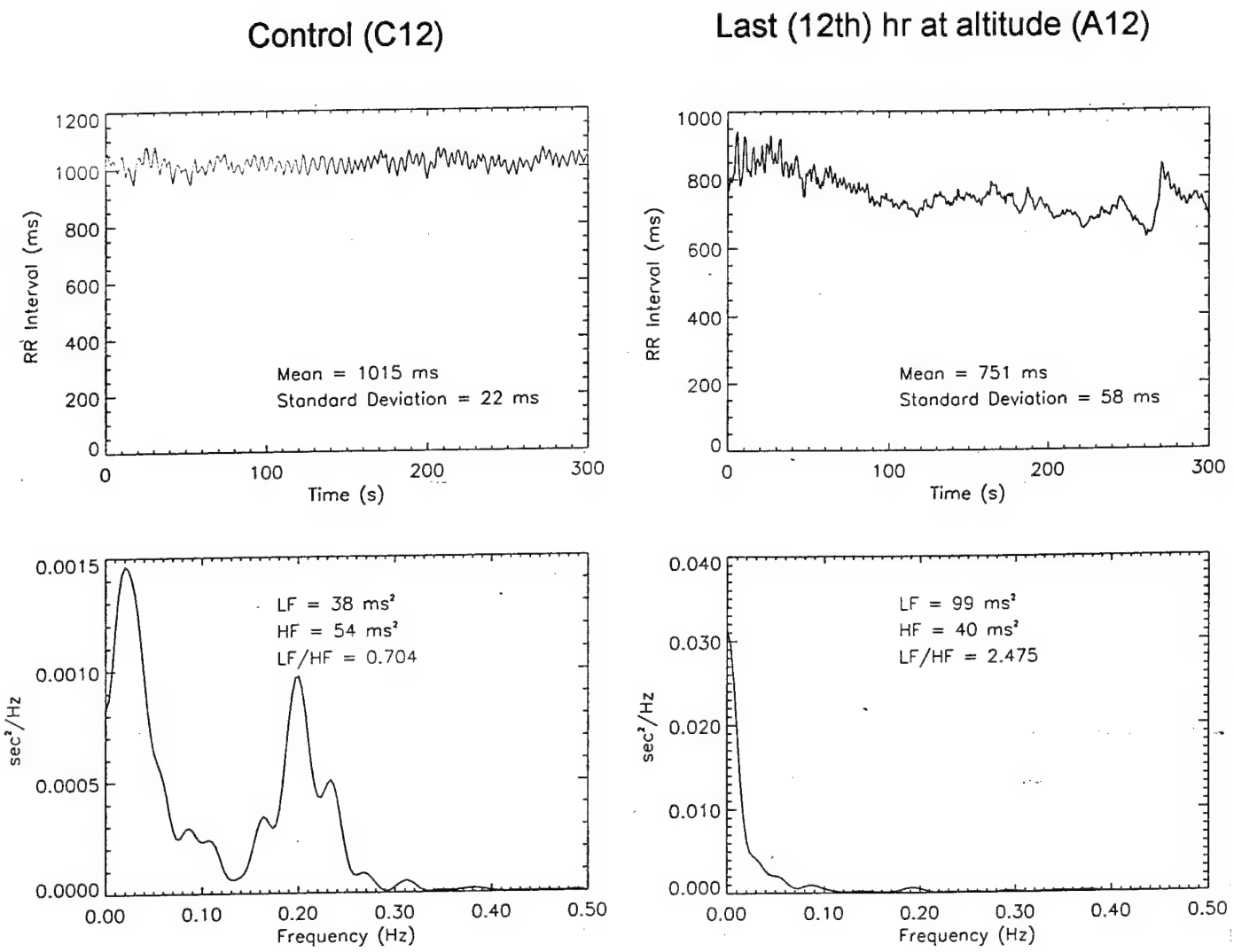


Fig. 13. Recording of a subject at C12 and A12. Upper recording is 5-min tachogram; lower recording is frequency spectrum. Note different scale on Y-axes.

analyze results in terms of total sympathetic tone and sympathetic/parasympathetic (vagal) balance. The interpretation of the relationships between sympathetic and vagal tone and the quantification of the frequency components remain somewhat controversial. However, there seems to be general agreement that (a) the LF/HF ratio is directly related to the degree of sympathetic/vagal balance of heart rate control by the autonomic nervous system and (b) that the total variability (power) of LF plus HF is inversely related to general sympathetic tone because HR variability is reduced by sympathetic tone. The area under the frequency domain curve is the variance of the R-R intervals.

Because each individual has peculiarities in physiological variations in ventilatory rhythm, vasomotor waves and other modulating CNS oscillations, it is preferable that HRV parameters of all subjects are compared to their own control (C12) conditions. Because of technical difficulties and after prescreening the recordings for non-physiological artifacts, adequate quality data were obtained from 70% of the recordings.

In order to determine whether the LF/HF ratio and LF+HF power was related to AMS from the available data, we chose 13 individuals who had the highest AMS score (sick) at A12 in one of their runs (if more than one) and the 13 who had the lowest run score (nonsick). The HRV results for these two groups are shown in Table 16-appendix for C12 (control) and A12. The mean AMSa in the nonsick and sick was 1.5 and 7.3, respectively ($P<0.001$). Table 16-appendix shows the mean R-R interval (ms), the SD (square root of the variance), the coefficient of variation, the LF and HF components of the curve areas (ms^2) and the LF and HF components in normalized units (nu). The latter are the percent of each relative to the total HF+LF area. This normalization eliminates the very low frequencies from the total area. The ratio of LF/HF is also presented.

The table on the next page summarizes the data from Table 16-appendix. It shows the mean change at altitude (A12 minus C12) for parameters in each group and the probability levels for the significance of the difference of these changes between the groups. Also shown are the P values for the significance of differences between C12 and A12 for all 26 subjects combined (All). In the nonsick group, the trends from C12 to A12 are as follows: a) the mean R-R interval decreased from 998 to 801 ms (heart rate increase from 60 to 75/min), b) the SD decreased slightly and the coefficient of variation remained about the same, c) the LF and HF components were both reduced at altitude, but the HF portion of the total HF plus LF area decreased proportionately more and d) this resulted in an increase in the LF/HF ratio. In the

parameters showing a difference approaching statistical significance between groups were the mean and SD, indicating that the sick subjects had a tendency to increase their heart rate more than the nonsick at altitude and reduce the total curve area (variance) more.

	Mean R-R	SD	C.V.	LF	HF	LF(nu)	HF(nu)	LF/HF
Nonsick	-197	-11	0.2	-175	-194	9	-9	0.63
Sick	-259	-26	-1.2	-512	-167	8	-8	1.07
Diff. (P)	0.15	0.19	0.34	0.32	0.86	0.91	0.91	0.67
All (P)	**<0.001**	**0.002**	0.46	**0.047**	**0.022**	0.06	0.06	0.10

The results, combining all 26 subjects, show that there was a significant increase in heart rate from C12 to A12 and that the variance of HR (total area under the power spectrum curve) is reduced by the 12th hr of altitude, with the LF component showing the greatest reduction in absolute values (Table 16-appendix). The coefficient of variation remained about the same. The LF and HF power components were both reduced significantly, with the altitude-induced changes in LF(nu) and HF(nu) being nearly significant. The LF/HF ratio also increased, but was not significant (P = 0.10). Although these findings are clearly associated with altitude exposure, there were no significant differences between the sick and the nonsick subjects in these parameters. These findings demonstrate that there is a general increase in total sympathetic tone and a shift in sympathetic/parasympathetic balance of HR control towards the former with altitude exposure. However, the degree of AMS at A12 is not significantly correlated with these changes. Insufficient HRV data were available to analyze altitude changes by the five subgroups. However, because AMS was not different between groups and since no statistical differences were noted between HRV parameters in the very sick and nonsick groups above, it is logical to conclude that HRV differences between groups would also not be notable.

It has been suggested that an increase in sympathetic drive during early altitude exposure may contribute to the subsequent development of AMS. The results above only show the control vs. 12 hr differences, therefore the changes from C12 to A1 (A1-C12 = Δ) in the LF/HF ratio with respect to subsequent peak AMSa score were also evaluated. No significant relationship was found between ΔLF/HF and AMSa for all the runs where HRV

records were available (n = 57, r = -0.06, P = 0.64). A significant positive relationship between the LF/HF ratio at A1 and A12 (n = 53, r = 0.33, P = 0.016) suggests that sympathetic/vagal balance remains proportionately similar within subjects over the time at altitude. A significant negative relationship between the LF/HF ratio at C12 and AMSa (n = 57, r = -0.26, P = 0.049) suggests that a greater baseline sympathetic/vagal balance may predispose subjects to be more tolerant to altitude.

If the plasma catecholamine levels and the LF/HF ratio and total LF and HF areas of heart rate variability are related to sympathetic drive then a relationship would be expected. The correlations between AMSa and both Norepi and Epi levels and LF/HF were evaluated. We considered the relationship between these variables in the 13 sick and 13 nonsick subjects in Table 16-appendix. No significant relationships were noted between LF/HF and Norepi or Epi levels at C12 and A12, (r = 0.07 and 0, respectively). The early sympathetic response, defined as ΔLF/HF and ΔNorepi or ΔEpi, also showed no clear relationship (r = 0.08 and 0.06, respectively). A correspondence, but not a significant relationship was noted between catecholamines and the sum of LF and HF (inversely related to sympathetic drive) from the data in Table 16-appendix. The r-value between LF+HF and Norepi was –0.18 (P = 0.22), for LF+HF and Epi it was –0.25 (P = 0.08) and between the sum of Norepi and Epi it was -0.19 (P= 0.19). These results indicated some correspondence between HRV indices and plasma catecholamine levels, but were not significant, as often presumed. The following hypotheses can be addressed:

Hypothesis 4. Increased sympathetic nervous system activity precedes fluid retention and AMS, and is independent of menstrual cycle phase. Cumulative fluid retention was significantly larger in F than in L, but the early (first hour) Norepi and Epi responses to altitude were very similar in these two groups (Fig. 12-page 62). Furthermore, the sympathetic stimulation inferred from HRV changes from C12 to A1 was also not related to AMS severity in the table on the previous page. Therefore the first part of the hypothesis can be rejected, as there is no basis for a direct relationship between the early rise in sympathetic tone and fluid retention. On the other hand, there is no basis to reject the second part of the hypothesis, stating that the sympathetic response is independent of cycle phase, because the responses in catecholamines were not different between L and F.

Hypothesis 9. Increased sympathetic nervous system activity precedes fluid retention and AMS independent of oral contraceptive use. The first part is rejected (on the same basis as above). Fig. 12 shows that there is a smaller early response in Norepi during C and P than in L and F and that the Epi response is also lower in P. Yet the average AMS was

slightly higher (not significant) on OCPs. On the other hand, there is no basis to reject the second part of the hypothesis, stating that the sympathetic response is independent of OCPs, because the responses of catecholamines were not significantly different between the OCP and menstrual cycle experiments.

The relationships between HRV and catecholamines seem tenuous at best. Few significant differences were noted between catecholamine levels in the subgroups in Tables 15A, B and C-appendix and no clear differences were seen in HRV parameters between sick and nonsick subjects in Table 16-appendix. These observations suggest that there are no clear differences in early sympathetic responses between gender, menstrual cycle women or women taking OCPs to account for variations in AMS or serve as prognosticators for AMS.

Magnetic Resonance Imaging (MRI)

In 91 of the 100 experiments, MRI measurements of the head were made as the last experimental procedure on the control day and after the altitude chamber day, when many of the subjects were still experiencing severe AMS. The omitted experiments resulted because of emergency clinical demands of the magnet or MRI technician. The runs omitted were mostly for women who were being tested at altitude the third or fourth time. The MRI experiments were performed in a Picker, 1.5T whole-body magnet. The parts of the analysis that are operator-dependent have the operator blinded to which part of the protocol the images came from. All signal intensity values were standardized by signal intensities from water bottles included in each imaging data set.

The collected MRI data included:

a) T_1-weighted, 3-D data sets,
b) A series of T_2-weighted image slices through the cerebellum and cerebrum,
c) A series of magnetization transfer contrast (MTC) slices through the same regions,
d) T_2 and MTC image intensity data sets within the genu and splenium regions of the corpus callosum from optimal image slices of these regions. Increased T_2 signal intensity with severe AMS in these regions has been reported by Hackett, et al (37).

T_2 magnetic resonance imaging is sensitive to the chemical environment of water protons in the body. Variation in the water content and the chemical environment of tissue will lead to differences in the magnetic relaxation characteristics of the protons and change the signal intensity of the tissue. Magnetization transfer contrast (MTC) imaging depends on

proton-to-proton interaction with transfer of magnetization from one nucleus to another nucleus. MTC imaging is sensitive to the number of proton interactions that can occur in different tissues of the body. Increased water content in a region of tissue allows increased freedom of water movement and proton-to-proton interaction. Therefore, MTC imaging is dependent on a different aspect of tissue water content than T_2 imaging, and can be more sensitive to the development of tissue edema.

The T_1-weighted 3-D data sets were used to orient the slice selection so that the slices matched on the control and post-altitude studies. The T_2-weighted and MTC-weighted images were placed and oriented in the same region of the brain for each study by localizing the slices using landmarks from the T_1, 3-D data set.

CSF Volume Measurements: The objective was to determine whether there was a significant change in brain CSF volume between images taken on the control day and after the high altitude exposure. The assumption was that an increase of brain swelling would be reflected by a corresponding reduction in CSF volume.

CSF is characterized by long T_2 values and it appears bright in long echo time images. Gray matter appears darker and white matter is even darker. The field of view was 29.5 cm, and the image size was 256 x 256, giving a resolution of 1.152 mm. The CSF was calculated using a T_2 image derived from a multiple echo (30, 60, 90 and 120 ms) data set of T_2 measurements. We collected 20 axial slices, each 5 mm thick. The CSF detection algorithm from T_2 incorporated the following steps:

a) Intensity normalization: The user manually marked the calibration bottle and the intensity of the images was normalized to the bottle intensity.

b) T_2 calculation: T_2 images were calculated for each of the 20 slices by fitting an exponential Ie^{-T_e/T_2} to the image intensity (I), voxel-by-voxel to the four images at different echo times, where T_e is the echo time. The output of this calculation was two images, a T_2 image and a corrected proton density image (I).

c) Data set for CSF segmentation: A new data set was assembled, consisting of 20 slices of T_2 images and 20 slices of corrected proton density images, (I). The CSF was marked manually in different parts of these images and in different subjects based on anatomical considerations and typical ranges for T_2 and intensity (I) in these images were obtained.

d) CSF segmentation: A region with $T_2 > 320$ ms and $I > 100$ was marked as consisting of 100% CSF. Regions with $100 < T_2 < 320$ and $I > 100$ were marked as consisting partially of CSF (see f below).

e) Elimination of non-CSF regions: Regions such as eyes, calibration bottles and image noise outside the brain image that was characterized as CSF, were manually excluded from CSF volume calculations.

f) Partial volume calculation: Partial volume was modeled as a mixture of two types of material, the CSF as region '1' and white matter as region '2'. In a voxel, let f_1 and f_2 be the fractions of the two materials, *I*(1) and *I*(2) be the proton density and $T_2(1)$ and $T_2(2)$ be the two transverse relaxation times. Then for the mixture (*m*) with proton density *I*(*m*) and relaxation time $T_2(m)$ we have

$$\frac{I(m)}{T_2(m)} = \frac{f_1 I(1)}{T_2(1)} + \frac{f_2 I(2)}{T_2(2)}, \qquad [1]$$

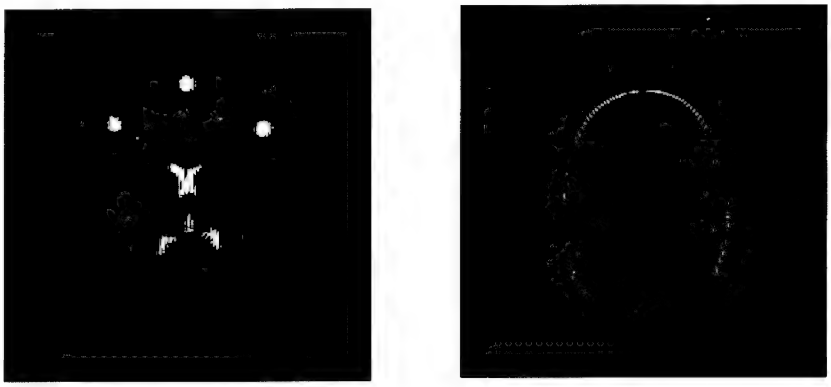
where $f_1 + f_2 = 1$. It follows from the above equation that

$$f_1 = \frac{\frac{I(2)}{T_2(2)} - \frac{I(m)}{T_2(m)}}{\frac{I(2)}{T_2(2)} - \frac{I(1)}{T_2(1)}}. \qquad [2]$$

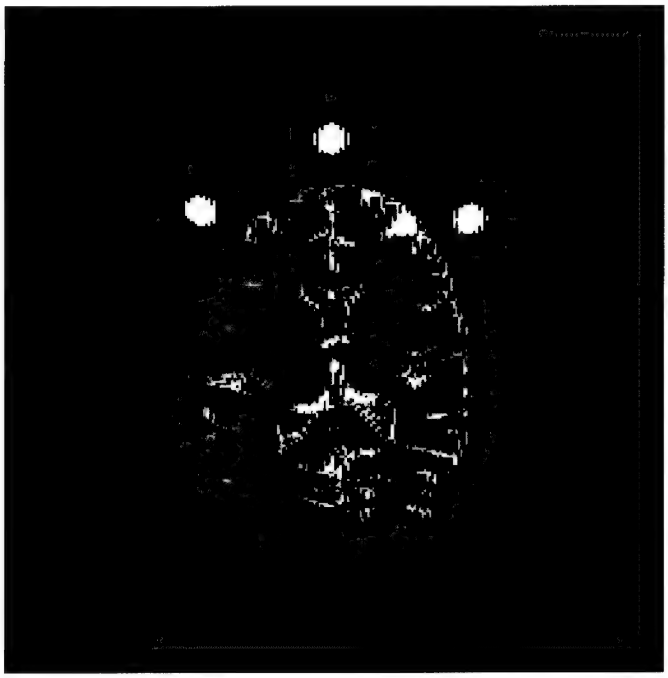
The average values for $\frac{I(2)}{T_2(2)}$ = 3.5 for white matter and $\frac{I(1)}{T_2(1)}$ = 0.73 for the CSF, were calculated from the data of 10 subjects. $I(m)$ and $T_2(m)$ are the values calculated in step (b) above. In the region where T_2 > 320 ms the CSF fraction was taken as 1.0 and for 100< T_2 <320 it was calculated from Eq. [2] above. The total CSF volume was obtained by summing the products for all the relevant pixels for each total fraction X the pixel volume of 0.00663 cc. An actual image slice is shown on the next page (Fig.14), indicating the CSF segmentation procedures.

The method to calculate CSF volume from MTC was similar to that used for calculating CSF volume from T_2 data. Twenty, 5 mm thick, slices were taken with MTC contrast and 20 slices at the same locations without MTC contrast. These are standard MRI pulse sequences on the 1.5 T Picker whole body imaging system. The CSF and other fluid-like tissue appear brighter in images with MTC contrast. For CSF detection from magnetization transfer contrast (MTC) The following steps were utilized:

TE = 30 ms TE = 60 ms TE = 90 ms TE = 120 ms



T_2 Image Proton Density Image



CSF
(Blue - 100% CSF, Yellow - Partial CSF)

Fig. 14. Method for CSF segmentation.

The top row shows the four images taken at echo times of 30, 60, 90, and 120 ms. The CSF appears brighter in the 120 ms echo time image because it enhances tissue with long T_2. The second row shows the calculated T_2 and the proton density image from the images of the first row. The CSF shows up clearly in the T_2 image. The image in the last row shows the results of the segmentation algorithm with blue being 100% CSF and yellow as partial volume CSF. Note calibration bottles in images.

a) Intensity normalization: The user manually marked the calibration bottle and the intensity of the images was normalized to the bottle intensity.
b) Relative MTC contrast: The ratio of images with MTC contrast to those without MTC contrast was taken. These ratio images (R) were the data set for CSF segmentation.
c) CSF segmentation: A region with R > 0.75 was marked as consisting of 100% CSF. Regions with 0.55 < R < 0.75 were marked as consisting of partial CSF volume with white matter. These ranges were chosen from average values of CSF and white matter in 10 images.
d) Elimination of non-CSF regions: Regions such as eyes, calibration bottles and image noise outside the brain image that was characterized as CSF, were manually excluded from CSF volume calculations.
e) Partial volume calculation: We assumed that the relative MTC contrast depended linearly on CSF volume. The CSF fraction, f_1 ,in a partial volume was taken as

$$f_1 = \frac{R(m) - 0.55}{(0.75 - 0.55)}, \qquad [3]$$

where R(m) is the relative MTC contrast in the partial volume region.
f) The total CSF volume was obtained similarly to T_2 by summing the products for the relevant pixels.

MRI Results

All MRI scans were evaluated by a Board-certified neuroradiologist for clinically significant structural abnormalities and for qualitative evidence of cerebral edema. None of the subjects exhibited any abnormalities that could be construed as having resulted from the exposures to hypoxia and all the findings noted have been categorized as being within the recognized deviations of normal.

In order to determine whether the T_2 and MTC estimates of CSF volume and corpus callosum image intensity were quantitatively different between subjects who had AMS and those who did not, we employed the following steps: First, we ranked all experiments according to AMS severity (AMSa score). Then we selected the 13 individuals appearing in the upper quartile of the rank order (highest score, n=13, denoted as "sick") and the 13 appearing in the lower quartile ("nonsick"). We then compared the differences in CSF volume and signal intensity in the corpus callosum regions between the control (C12) and the post-

altitude measurements (A12) in these two groups of subjects. The results are shown in Table 17A-appendix for T_2 and 17B-appendix (for MTC). The mean CSF volume in all 26 subjects by T_2 analysis was 144 ml (SE = 9 ml) before altitude and 135 ml after altitude exposure. This value for CSF volume compares well with the average of 154 ml reported for men and women by Matsumae et al. (38). This significant ($P<0.001$) 10 ml reduction in CSF volume by altitude exposure may indicate a corresponding 10 ml increase in brain volume resulting from edema of the brain. This reduction in CSF volume was very similar in the sick and nonsick subjects and therefore any brain edema inferred due to hypoxia can not be implicated as a cause of AMS based on these data. A recent report of a study by USARIEM (39), found with MRI scans that brain volume increased by 26 ml in seven male subjects after exposure to 430 mm Hg in a decompression chamber for 32 hr. They also found no relationship between this volume change and AMS scores. That study and ours indicate that either MRI is not sensitive enough to measure brain edema that is specifically associated with early AMS, or that global brain edema is not associated with early AMS. The decrease in CSF volume that was noted with T_2 imaging in our study was confirmed by MTC signal processing (Table 17B-appendix, mean = 9 ml, $P = 0.007$). The r-value for ΔCSF by T_2 and MTC for all 26 subjects was 0.43, $P = 0.030$), showing that the tissue boundary selection criteria were reasonably consistent between the two signal processing procedures. However, the mean pre-altitude CSF volume was 24 ml less by MTC. The r-values for pre- and post-altitude CSF volumes were 0.95 and 0.96, respectively.

The T_2 and MTC image intensity estimates in the splenium and genu regions of the corpus callosum did not demonstrate significant differences as a result of altitude exposure. Increased T_2 intensities have been reported by clinical MRI studies in the corpus callosum, especially the splenium, in patients suffering from very severe AMS and pulmonary edema (37). The difference between sick and nonsick subjects was nearly significant in the splenium for MTC (Table 17B-appendix), however this change was in the direction of a reduced intensity in the sick subjects after altitude exposure, so is supportive of a negative finding in this region. The r-values for the 26 MTC vs. T_2 values for pre-altitude, post-altitude and the difference raged from –0.02 to –0.44, indicating that these estimates of "water" intensity were relatively independent.

The pre- and post-altitude MRI scans of the 13 sick subjects were also given to a senior neuroradiologist in blinded fashion in order to attempt a differentiation of the order of each subject's scans (pre or post). Prior to this the neuroradiologist was shown the original brain MRIs, previously taken from seven patients with severe mountain sickness and pulmonary

edema (37) for familiarization of these clinical MRI features of severe cerebral edema. In no case was a definitive distinction made between the pre- and post-altitude MRIs.

Based on these clinical observations and the quantified data in Table 17-appendix, no differences in brain edema resulting from altitude exposure in these sick and nonsick subjects selected from the opposite ends of the AMSa continuum were found. Therefore, the following two hypotheses cannot be accepted:

Hypothesis 11. Cerebral edema as determined from MRI will be greater during the follicular phase of the menstrual cycle and will be associated with more severe symptoms of AMS and fluid retention. Fluid retention was significantly higher in the follicular phase, as shown previously, but AMSa was not significantly higher, and because there was no indication of cerebral edema in the most sick subjects, this hypothesis can be rejected.

Hypothesis 12. Cerebral edema as determined from MRI will be greater in females not taking oral contraceptives compared to the same females when they are taking oral contraceptives and will be associated with more severe symptoms of AMS. Because AMS symptoms were not lower in women taking OCPs and since there was no indication of cerebral edema in the sickest subjects, this hypothesis can be also be rejected. Hypothesis 15, also related to cerebral edema, can be tentatively accepted:

Hypothesis 15. Cerebral edema as determined from quantitative MRI will be the same in women with AMS compared to age-matched, men with AMS. This hypothesis can be accepted, since no cerebral edema differences could be inferred from Table 17-appendix in the very sick subjects, because the ΔCSF volume was similar to the nonsick subjects. The mean of the T_2 and MTC values for ΔCSF volume in the 3 males was –5 ml and for the 10 women it was -13 ml. These differences did not approach statistical significance (P = 0.22).

Cognitive Function Tests

The cognitive function tests included the following seven tests as part of the Walter Reed Performance Assessment Battery (PAB) of tests utilized by the Army (40):

a) Logical Reasoning (LogReas)
b) Stanford Sleepiness Scale
c) Choice Reaction Time (ChoiceRT)
d) Profile of Mood States
e) Stroop

f) Code Substitution (CodeSub)

g) Delayed Recall (DelRec)

All of these tests were performed serially, in the sequence listed, at C12, A1, A6 and A12. Prior to performing the tests at C12, each subject was given the test a total of 10 times for practice in the chamber at ambient pressure to prevent the well-known learning curve to affect the serial results. The results for tests b, d, and e were omitted from analyses because "CodeSub" was deemed to measure attributes similar to the "Stroop" test and it seemed desirable to state the cognitive function in terms of reaction time and decision-making measures, independent of mood and sensations of sleepiness. Results of mental performance testing at altitude, and how results relate to AMS have been shown to be quite variable (41).

For each of the four tests we analyzed the test result for the "throughput" value, which is based on both the speed and accuracy of the responses and is calculated as the fraction of responses correct, multiplied by the speed of the responses (responses/min). For each of the four tests, a higher value is associated with a better mental performance. The results are summarized in the table below:

Mean "throughput" results of four cognitive function tests for five groups and correlations of score changes at altitude with AMSa.

	Test	C12	A1	A6	A12	A12-C12	A12-A1	A6-A1
Men	ChoiceRT	74.4	75.7	74.9	74.2	-0.17	-0.18	-0.22
n = 18	LogReas	15.5	15.3	14.0	16.0	0.42	0.31	-0.25
	DelRec	32.0	37.1	32.3	35.8	-0.08	0.11	0.16
	CodeSub	26.0	27.1	24.3	28.2	0.06	0.04	-0.12
Follicular	ChoiceRT	83.0	83.8	85.4	84.5	-0.09	-0.42	-0.51*
n = 20	LogReas	16.0	17.1	17.9	18.0*	-0.13	-0.27	-0.35
	DelRec	42.4	37.8	32.1*	46.2#	-0.26	-0.25	-0.11
	CodeSub	36.4	33.8	31.0	35.0	0.01	-0.07	-0.08
Luteal	ChoiceRT	83.3	82.9	83.5	84.1	-0.29	-0.33	-0.10
n =18	LogReas	17.5	16.9	17.8	19.3#	-0.35	-0.13	-0.05
	DelRec	45.0	39.1	35.3*	40.3	-0.30	-0.34	0.06
	CodeSub	35.6	32.4	31.2*	32.8	-0.03	0.05	-0.21
Placebo	ChoiceRT	83.5	84.9	83.7	83.3	-0.21	-0.08	0.02
n = 19	LogReas	19.6	18.9	18.4	18.3	-0.24	-0.04	0.02
	DelRec	45.6	48.7	43.7	50.9	0.05	0.06	0.04
	CodeSub	41.0	39.3	38.1	39.4	-0.42	-0.07	-0.29
Pill	ChoiceRT	84.1	83.8	81.3	80.0#	-0.47*	-0.22	0.38
n = 20	LogReas	18.8	16.8	16.9	18.0	-0.37	-0.18	0.17
	DelRec	40.5	43.1	43.3	41.0	-0.22	-0.36	-0.12
	CodeSub	40.0	36.9	36.4	37.3	-0.27	-0.31	-0.17
All	ChoiceRT	81.8 (15.9)	82.3 (16.4)	81.9 (15.1)	81.3 (16.2)	-0.23*	-0.23*	-0.09
n = 95	LogReas	17.5 (6.5)	17.0 (6.4)	17.0 (6.4)	17.9#(6.0)	-0.15	-0.06	-0.13
	DelRec	41.2 (18.7)	41.2 (16.9)	37.4#(15.8)	42.9 (16.8)	-0.13	-0.14	0.02
	CodeSub	36.0 (11.8)	34.0*(9.6)	32.3*#(9.9)	34.7 (8.8)	-0.12	-0.09	-0.16

( ): SD for all 95 scores

*: P<0.05 vs. C12, or r-value significant at P<0.05

#: P<0.05 vs. A1

From the SD values given for all subjects at the bottom of the table, it is evident that the largest scatter shown between subjects was in DelRec (CV = 42%) and the most consistent results were seen in ChoiceRT (CV = 9%). It is also clear from the table that the women performed substantially better than men for all four tests. Only at A6 for DelRec were the men equal to the follicular women. At C12 all four tests scores were better for women, with P-values for significance of differences vs. men ranging as follows:
ChoiceRT: 0.11 for follicular to 0.06 for pill;
LogReas: 0.82 for follicular to 0.08 for placebo;
DelRec: 0.13 for pill to 0.032 for luteal (P = 0.049 for placebo);
CodeSub: All values for women better at P = 0.008 or less.

For all the subjects, the change in scores from C12 to A12 was negatively correlated with AMSa, indicating that overall the test performances deteriorated as AMS became more severe. However, this relationship was significant only with the ChoiceRT test (r = -0.23, P=0.024) and was of equal significance when comparing the change in these test scores from A1 to A12. The correlation with AMSa was lowest when compared with the change in scores from A6 to A1. There was no consistent change in scores from C12 to A12, as choiceRT and LogReas remained about the same over the serial measurements, DelRec fell significantly from A1 to A6 and then returned to values above baseline by A12 and CodeSub declined by A1 and further by A6 and then partially recovered. In some of the tests within groups there were significant improvements in performance with time at altitude (DelRec in F and LogReas in L), while others tests showed a reduction (ChoiceRT in the pill experiments).

In comparing the changes in the four test scores from C12 to A12 between F and L, the largest difference was noted for DelRec, where in F the score increased by 3.8 and in L it decreased by 4.7. This difference was not statistically significant by paired-t test. Differences between P and C also were not significant. The remaining two hypotheses can now be addressed:

Hypothesis 5. Cognitive impairment precedes symptoms of AMS independent of menstrual cycle phase. Mental performance changes with time at altitude were not significantly different in the two cycle phases, so that part of the hypothesis can be accepted. For the first part of the hypothesis to be true, the correlation between AMSa (determined for A12) would have to be more negative vs. A6 minus A1 score differences than vs. A12-A1 score differences. The average r-values from the table on the previous page for the four tests

are the same for A12-A1 as for A6-A1 in F. In L, the corresponding mean r-values are –0.19 and –0.08. This shows that cognitive impairment does not precede AMS and this notion can be rejected. Also, there was usually an increase in the four test scores from A6 to A12, while AMS become worse in susceptible subjects (Table 1B-appendix).

Hypothesis 10. Cognitive impairment will be improved in women who are taking oral contraceptives and will be associated with less cerebral edema compared to when they are not taking oral contraceptives. There was no evidence of cerebral edema from the MRI measurements in any group of subjects in relation to AMS symptoms, so there is no basis to accept the second part of this hypothesis based on this study. The average change in the four cognitive tests was 0.1 in the menstrual cycle women (average of F and L) and –0.7 in the OCP runs (average of placebo and pill runs). This means there is also no statistical basis to accept the first part of the hypothesis.

In summary, the cognitive test performances are inversely related to AMS symptoms, but the significance is borderline and was significant in only one of the four tests. The observation that the average scores did not decline while AMS symptoms increased, indicates that this 12-hr altitude exposure was not associated with a clear deterioration in cognitive function as measured by these tests.

Key Research Accomplishments

The statement of work, as originally proposed, is listed below:

Technical Objective 1: To determine if the symptoms of AMS are altered by the luteal and follicular phases of the menstrual cycle.

Task 1: Months 1-2: Identify pool of potential subjects. Begin basal temperature monitoring.

Task 2: Months 3-4: Begin progesterone screening; develop first menstrual cycle map for each subject. Practice all experimental procedures with subjects.

Task 3: Months 4-16: Complete two chamber exposures in 18 women, once each during the luteal and follicular phases of the menstrual cycle.

Task 4: Months 4-16: Complete one chamber trial on nine of the 18 men in the age-matched control group.

Task 5: Months 5-18: On-going data entry, laboratory analyses.

Task 6: Months 18-24: Data analysis, report and manuscript preparation.

<u>Technical Objective 2</u>: To determine if the symptoms of AMS are less severe in women taking oral contraceptives compared with the same women when they are not taking oral contraceptives.

Task 7: Months 16-24: Recruit subjects interested in participating in two studies separated by at least six months.

Task 8: Months 20-25: Complete first altitude study on all 18 women.

Task 9: Months 26-31: Complete second altitude study on all 18 women.

Task 10: Months 4-16: Complete one chamber trial on second nine of the 18 men in the age-matched control group.

Task 11: Months 28-32: On-going data entry and laboratory analyses.

Task 12: Months 31-36: Data analysis, report and manuscript preparation.

All of the above tasks have been completed, essentually on schedule. Included with this report is a disk containing this report and the raw data on which it is based. The following are somewhat simplified summary observations emanating from this study. They must be considered within the limits of this study in terms of the subject population, time and degree of altitude exposure and the measurement techniques utilized.

- There is no difference in the incidence of AMS between men and women and menstrual cycle phases in women.
- The use of oral contraceptives does not affect the incidence of AMS or prevent it.
- Caloric intake is reduced by 25% during a 12-hr altitude exposure, the reduction is directly related to the degree of AMS experienced.
- Men and women respond about equally to a cold pressor test. Responses are not related to menstrual cycle phase or the use of oral contraceptives in women and are of no value in predicting AMS.
- Pulmonary ventilation is greater in the luteal than follicular phase during altitude exposure.
- The ventilation response to altitude is not related to AMS severity or short hypoxic response tests when not at altitude.

- Women have a higher ventilation than men in relation to metabolic rate. This higher ventilation is not solely the result of higher progesterone.
- Early AMS is not associated with changes in pulmonary gas exchange or ventilation/perfusion heterogeneity. It is associated with clinically insignificant hypoxemia.
- Pulmonary interstitial edema during early AMS may account for a small reduction in voluntary maximal airflow.
- Body temperature increases at altitude. It increases less in subjects who experience more AMS.
- Neither altitude exposure nor AMS are associated with a change in the transcapillary exchange rate of albumin.
- Total body water and extracellular water increase with AMS and plasma volume is reduced by altitude, but the plasma volume change is not clearly associated with AMS.
- Fluid retention because of a decrease in urine flow is directly related to AMS.
- Fluid retention at altitude is greater in the follicular phase in women than in the luteal phase or in women taking oral contraceptives or men.
- AMS is associated with a rise in plasma aldosterone, antidiuretic hormone and atrial natriuretic peptide.
- Plasma aldosterone is doubled during baseline and altitude in the luteal phase as compared with the follicular phase and men and also elevated by exogenous progesterone when on oral contraceptives.
- Plasma renin activity is higher during baseline and altitude in the luteal phase as compared with the follicular phase and also elevated by exogenous progesterone when on oral contraceptives.
- Plasma catecholamines show variable responses to altitude and changes are not clearly related to AMS.
- Heart rate variability analyses demonstrates an increase in sympathetic tone at altitude, independent of AMS.
- The sodium/potassium ratio in urine increases with AMS severity.
- A small reduction in CSF volume, with presumed brain swelling, occurs after altitude exposure, but is not associated with AMS.
- Women perform better than men on mental performance tests at baseline and altitude.
- AMS is directly associated with a small decline in mental performance.

CONCLUSIONS

In 18 men and 33 women volunteers, aged 19-38 yr, the expected range of AMS scores was observed when randomly selected individuals are exposed to simulated altitude of 16,000 ft. Significant AMS was noted in 63% of the experiments within the 12-hr exposure. No significant difference in AMS susceptibility between men and women was demonstrated. There was no difference in the severity of AMS symptoms during the luteal and follicular phases of the menstrual cycle in women and the results showed that taking oral contraceptives would not reduce AMS symptoms. Women performed significantly better on cognitive function tests at baseline and altitude than men. Results pertaining to differences in altitude-induced changes in ventilation, blood gases, fluid balance and body water compartments between subject groups were unimpressive, however women in the luteal phase increased their ventilation more at altitude than when in the follicular phase. Decreased urine flow at altitude is associated with AMS more clearly in women who are not on oral contraceptives than in women who are on contraceptives and men. In general, fluid retention, with an increase in extracellular and total body water and reduced urine volume, was directly related to AMS severity. The transcapillary exchange rate of circulating albumin was not altered at altitude and variations in it and plasma volume changes are probably not responsible for the development of AMS. The arterial blood gas measurements demonstrated that pulmonary gas exchange was not diminished significantly during the 12 hr at altitude, even in subjects with severe AMS. Altitude illness did not correlate with changes in ventilation at altitude or acute hypoxic ventilatory responses at baseline. Sympathetic nervous system changes at altitude, estimated from heart rate variability and catecholamines, were not clearly associated with AMS and responses to baseline cold pressor tests are not valid predictors of AMS. Body temperature increased at altitude and this rise correlated significantly, but inversely, with AMS. Also, brain CSF volume decreased slightly with altitude exposure, but this reduction was not associated with AMS. The rise in fluid-regulating hormones, ADH, aldosterone and ANP, continued in AMS-prone subjects while in a state of fluid overload. The response of these hormones to acute hypoxia and fluid manipulations in AMS-prone and tolerant subjects could be further explored as potential pathophysiological mechanisms of AMS.

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APPENDICES

Four Appendices follow:

Appendix 1: 17 tables

Appendix 2: List and order of technical tasks to collect raw data

Appendix 3: Articles, abstracts, presentations

Appendix 4: List of personnel

Appendix 1

17 TABLES OF DATA TO GO WITH TEXT

Generally, Tables "A", "B" and "C" refer to men, menstrual cycle (follicular-"F" and luteal-"L") and women on oral contraceptives (placebo-"C" and pill-"P") groups, respectively.

Table 1A. Age, VO2max, %fat and Lake Louise symptom scores of 18 men.

Subj. #	Age	VO2max	% Fat	VO2/LBM	A0	A1	A6	A12	Peak AMS	peak HA	AMSa
0	27	45	14	60	**1**	3	3	8	8.0	3	7.77
1	32	55	11	62	**1**	**3**	5	7	7.0	2	6.30
3	25	50	12	56	0	0	0	0	0.0	0	0.76
5	23	32	24	42	0	0	**6**	9	9.0	3	7.61
7	30	52	8	56	0	0	2	3	3.0	2	3.12
9	30	40	8	44	0	0	5	7	7.0	2	5.77
10	27	39	25	52	0	**1**	6	11	11.0	3	9.83
12	21	44	20	55	0	**1**	3	5	5.0	2	3.93
14	29	54	8	59	0	0	0	1	1.0	1	1.18
15	27	59	10	66	0	**1**	0	1	1.0	1	1.26
17	25	31	18	37	0	1	3	**1**	2.0	1	1.79
19	27	50	11	56	0	0	**1**	0	0.5	0	0.94
20	32	43	11	48	0	0	**1**	**1**	1.0	0	1.40
22	32	48	17	57	0	0	3	5	5.0	3	4.42
24	27	50	6	53	0	3	5	6	6.0	2	5.35
25	23	37	19	45	0	0	**4**	7	7.0	2	7.74
27	29	53	9	58	0	**1**	0	0	0.0	0	0.67
28	27	57	2	59	0	0	2	6	6.0	3	5.26
Mean	**27**	**47**	**13**	**54**	**0.1**	**0.8**	**2.7**	**4.3**	**4.42**	**1.7**	**4.17**

A0: AMS score prior to entering chamber
A1, A6, A12: AMS score at hr 1, 6, and 12 (or last) at altitude
Bold: Headache score was zero
VO2max: ml/min/kg
HA: headache score

Table 1B. Age, VO2max, %fat, serum progesterone (ng/ml) and Lake Louise symptom scores of 21 women during follicular (F) and luteal (L) phase.

Subj. #	Age	VO2max	% Fat	VO2/LBM	Prog	A0	A1	A6	A12	Peak AMS	peak HA	AMSa
2F	33	33	28	46	0.3	0	0	**2**	3	3.0	1	2.51
2L					11.4	0	**1**	**1**	**1**	1.0	0	0.70
4F	26	33	33	49	0.3	0	1	3	1	2.0	1	2.11
4L					12.8	0	**1**	3	3	3.0	1	3.53
6F	28	37	28	52	0.4	0	0	1	3	3.0	2	2.40
6L					9.3	0	0	0	1	1.0	1	1.19
8F	24	37	32	54	0.2	0	0	**6**	**6**	6.0	0	5.92
8L					7.2	0	**1**	**5**	**5**	5.0	0	5.00
13F	33	32	22	41	0.3	**1**	**1**	2	2	2.0	1	1.15
13L					15.7	0	0	**1**	2	2.0	1	1.25
16F	28	36	31	52	0.4	**1**	0	**5**	4	4.5	1	4.98
16L					8.8	0	0	**2**	5	5.0	1	4.09
18F	23	45	20	56	0.5	0	0	**1**	**1**	1.0	0	0.58
18L					11.9	0	**1**	5	4	4.5	1	3.72
21F	24	48	16	57	0.7	0	**1**	3	4	4.0	2	3.65
21L					6.6	0	0	3	6	6.0	2	4.98
29F	29	34	36	53	0.4	0	0	1	1	1.0	1	1.40
29L					9.8	0	0	0	1	1.0	1	1.19
30F	26	29	30	41	0.4	0	0	**1**	4	4.0	2	4.31
30L					6.9	0	0	3	2	2.5	1	2.61
31F	26	48	25	60	0.3	**1**	1	1	2	2.0	1	2.11
31L					8.3	0	**1**	4	8	8.0	3	6.45
37F	23	51	20	63	0.3	0	0	4	4	4.0	1	4.57
37L					20.1	**1**	**4**	4	4	4.0	1	3.98
38F	28	38	26	51	0.4	0	**2**	4	11	11.0	3	10.18
38L					8.6	**2**	**4**	3	7	7.0	2	4.54
39F	29	23	39	36	0.4	0	4	8	8	8.0	2	7.22
39L					7.1	0	5	8	7	7.5	2	4.57
41F	32	29	33	43	0.4	0	0	0	**3**	3.0	0	3.20
41L					9.1	0	0	3	8	8.0	2	7.82
43F	22	48	18	59	0.5	0	0	3	2	2.5	2	2.66
43L					12.2	0	**2**	4	3	3.5	1	3.04
44F	29	27	44	48	0.3	**1**	**2**	3	10	10.0	3	8.37
44L					9.3	0	**1**	**4**	4	4.0	1	3.59
45F	33	34	27	47	0.2	0	0	6	12	12.0	3	9.70
45L					8.2	**1**	**2**	6	7	7.0	0	5.14
46F	23	39	22	50	0.4	0	0	**1**	4	4.0	1	3.61
46L					10.8	**1**	**1**	**2**	3	3.0	1	2.34
11F	32	33	21	42	0.3	0	0	**4**	3	3.5	1	4.00
11L												
23F	19	41	18	50	0.6	0	0	7	7	7.0	2	6.63
23L												
Mean F	**27**	**37**	**27**	**50**	**0.4**	**0.2**	**0.6**	**3.1**	**4.5**	**4.64**	**1.4**	**4.35**
Mean L	**27**	**37**	**28**	**50**	**10.2**	**0.3**	**1.3**	**3.2**	**4.3**	**4.37**	**1.2**	**3.67**

A0: AMS score prior to entering chamber

A1, A6, A12: AMS score at hour 1, 6, and 12 (or last) at altitude

Bold: Headache score was zero

VO2max: ml/min/kg

HA: headache score

Table 1C. Age, VO2max, serum progesterone (ng/ml) and Lake Louise symptom scores of 21 women on oral contraceptives during placebo (C) and pill (P) week.

Subj. #	Age	VO2max	% Fat	VO2/LBM	Prog	A0	A1	A6	A12	Peak AMS	peak HA	AMSa
4C	26	33	33	49	0.5	0	0	3	3	3.0	1	3.41
4P					0.3	0	0	3	3	3.0	2	3.59
6C	28	37	28	52	0.4	0	0	1	2	2.0	2	2.32
6P					0.3	0	0	0	1	1.0	1	1.19
16C	28	36	31	52	0.4	2	**2**	5	7	7.0	1	5.81
16P					0.4	0	0	**2**	**1**	1.5	0	3.55
21C	24	48	16	57	0.6	1	2	5	7	7.0	2	4.85
21P					0.6	**1**	**3**	4	7	7.0	3	5.74
29C	29	34	36	53	0.2	0	0	0	2	2.0	1	2.05
29P					0.2	0	**1**	**1**	0	0.5	0	0.89
32C	22	23	39	38	0.2	**1**	**2**	**4**	**1**	2.5	0	1.89
32P					0.3	0	**2**	3	4	4.0	2	3.75
33C	31	36	28	50	0.5	**2**	**2**	**1**	4	4.0	1	1.08
33P					0.4	**2**	**1**	7	7	7.0	2	4.97
34C	29	40	30	58	0.3	1	1	8	8	8.0	3	7.85
34P					2.4	0	**1**	3	3	3.0	1	3.62
35C	28	24	31	35	0.2	0	0	3	2	2.5	1	2.25
35P					0.3	0	1	**3**	3	3.0	1	4.38
36C	33	31	27	43	0.3	**1**	**1**	4	7	7.0	2	5.24
36P					0.2	0	0	**3**	5	5.0	2	3.78
37C	23	51	20	63	0.2	0	**1**	3	3	3.0	2	3.59
37P					0.5	0	0	4	6	6.0	2	5.47
38C	28	38	26	51	0.4	0	**2**	**3**	4	4.0	1	3.65
38P					0.4	2	4	**2**	**3**	3.0	0	3.40
40C	28	48	32	71	0.3	0	0	**2**	3	3.0	1	2.61
40P					0.3	0	**1**	**2**	5	5.0	1	5.19
42C	20	31	23	40	0.4	**1**	7	8	10	10.0	3	8.52
42P					0.2	**2**	5	5	6	6.0	3	7.91
44C	29	27	44	48	0.2	0	**1**	3	6	6.0	2	5.64
44P					0.2	0	0	6	6	6.0	2	5.77
45C	33	34	27	47	0.4	**1**	**2**	4	8	8.0	2	5.69
45P					0.2	0	0	7	10	10.0	2	8.00
47C	38	28	32	42	11.7	0	4	5	7	7.0	3	6.38
47P					13.1	0	0	4	7	7.0	3	5.80
48C	20	34	32	50	0.4	0	**2**	10	9	9.5	3	7.29
48P					0.4	**1**	5	5	8	8.0	2	7.27
49C	23	38	19	47	0.9	0	0	4	5	5.0	2	3.20
49P					0.5	0	0	3	4	4.0	2	3.54
50C	28	39	21	49	0.4	0	0	**1**	1	1.0	1	1.40
50P					0.3	0	0	**1**	0	0.5	0	0.88
26C												
26P	27	40	26	49	0.4	0	**1**	2	6	6.0	3	5.74
Mean C	**27**	**36**	**29**	**50**	**0.9**	**0.5**	**1.5**	**3.9**	**5.0**	**5.08**	**1.7**	**4.24**
Mean P	**27**	**36**	**29**	**50**	**1.0**	**0.4**	**1.2**	**3.3**	**4.5**	**4.60**	**1.6**	**4.50**

A0: AMS score prior to entering chamber

A1, A6, A12: AMS score at hour 1, 6, and 12 at altitude

Bold: Headache score was zero

VO2max: ml/min/kg

HA: headache score

Table 2A. Dietary variables for 18 men.

	CARBOHYDRATES (g)								FAT (g)								PROTEIN (g)							
Subj. #	prov	goal	prov/goal	24 hr	%eaten	con	alt	%diff	prov	goal	prov/goal	24 hr	%eaten	con	alt	%diff	prov	goal	prov/goal	24 hr	%eaten	con	alt	%diff
0	467	384	122%	361	94%	277	211	-24%	106	106	100%	72	68%	56	50	-11%	136	148	92%	83	56%	53	52	-2%
1	448	503	89%	448	89%	356	309	-13%	70	65	108%	70	108%	65	51	-23%	118	97	122%	118	122%	104	81	-23%
3	355	343	104%	355	104%	285	285	0%	76	77	98%	76	98%	69	69	0%	95	94	101%	95	101%	80	80	0%
5	339	282	120%	339	120%	303	186	-38%	90	88	103%	90	103%	65	22	-66%	134	133	100%	134	100%	95	38	-60%
7	470	451	104%	470	104%	368	368	0%	60	62	96%	60	96%	51	51	0%	132	126	105%	132	105%	113	113	0%
9	387	353	110%	387	110%	260	180	-31%	89	98	91%	89	91%	51	39	-23%	84	78	107%	84	107%	54	35	-35%
10	407	375	108%	335	89%	260	149	-43%	85	78	109%	79	102%	54	31	-42%	99	91	109%	99	109%	69	41	-41%
12	338	311	109%	338	109%	227	227	0%	74	69	107%	74	107%	25	25	0%	87	80	108%	87	108%	52	52	0%
14	534	493	108%	534	108%	392	392	0%	92	90	102%	92	102%	63	63	0%	139	149	93%	139	93%	101	101	0%
15	469	430	109%	469	109%	361	361	0%	78	86	91%	78	91%	69	69	0%	86	98	87%	86	87%	73	73	0%
17	379	311	122%	386	124%	274	234	-15%	76	82	92%	73	88%	58	52	-10%	79	83	95%	79	95%	57	48	-16%
19	479	428	112%	462	108%	328	249	-24%	83	79	106%	77	98%	60	51	-15%	120	113	107%	106	94%	86	65	-25%
20	265	212	125%	265	125%	202	202	0%	78	87	90%	78	90%	48	48	0%	70	65	108%	70	108%	53	53	0%
22	405	368	110%	405	110%	322	314	-2%	48	44	109%	48	109%	38	38	0%	83	78	106%	83	106%	53	52	-2%
24	296	264	112%	296	112%	225	153	-32%	58	60	97%	58	97%	45	32	-29%	58	54	108%	58	108%	46	26	-43%
25	426	408	104%	413	101%	316	316	0%	109	113	97%	99	88%	78	78	0%	88	82	107%	86	105%	58	58	0%
27	269	228	118%	269	118%	240	240	0%	44	47	93%	44	93%	28	28	0%	48	46	104%	48	104%	35	35	0%
28	459	429	107%	459	107%	359	230	-36%	87	87	100%	87	100%	78	50	-37%	108	98	110%	108	110%	96	49	-49%
Mean	400	365	111%	388	108%	297	256	-14%	78	79	99%	75	96%	56	47	-14%	98	95	104%	94	101%	71	58	-16%

	CALORIES								SODIUM (mg)								FIBER (g)							
Subj. #	prov	goal	prov/goal	24 hr	%eaten	con	alt	%diff	prov	goal	prov/goal	24 hr	%eaten	con	alt	%diff	prov	goal	prov/goal	24 hr	%eaten	con	alt	%diff
0	3365	3081	109%	2425	79%	1825	1500	-18%	4300	4377	98%	3500	80%	2610	2320	-11%	20	20	100%	17	85%	10	9	-10%
1	2900	2984	97%	2900	97%	2430	2015	-17%	4790	4795	100%	4790	100%	4210	3865	-8%	29	24	121%	29	121%	16	15	-6%
3	2480	2439	102%	2480	102%	2080	2080	0%	3140	2895	108%	3140	108%	2080	2080	0%	16	16	100%	16	100%	14	14	0%
5	2702	2453	110%	2702	110%	2179	1098	-50%	4633	4453	104%	4633	104%	3151	807	-74%	14	14	100%	14	100%	11	5	-51%
7	2948	2867	103%	2948	103%	2388	2388	0%	4680	5023	93%	4680	93%	3910	3910	0%	13	13	100%	13	100%	10	10	0%
9	2682	2606	103%	2682	103%	1712	1270	-26%	3520	3450	102%	3520	102%	1530	1270	-17%	17	16	106%	17	106%	10	6	-39%
10	2790	2566	109%	2450	95%	1660	1040	-37%	3545	3470	102%	3525	102%	1900	1150	-39%	12	12	100%	12	100%	8	6	-25%
12	2365	2185	108%	2365	108%	1340	1340	0%	4320	4190	103%	4320	103%	2405	2405	0%	17	16	106%	17	106%	10	10	0%
14	3520	3376	104%	3520	104%	2540	2540	0%	5780	5748	101%	5780	101%	2390	2390	0%	41	42	98%	41	98%	27	27	0%
15	2920	2891	101%	2920	101%	2355	2355	0%	3890	4234	92%	3890	92%	2860	2860	0%	32	28	116%	32	116%	19	19	0%
17	2510	2315	108%	2510	108%	1840	1590	-14%	3025	3039	100%	3015	99%	2105	1905	-10%	21	22	92%	21	92%	14	10	-30%
19	3150	2876	110%	2970	103%	2190	1710	-22%	4650	4450	104%	4410	99%	3610	3280	-9%	26	24	108%	25	104%	13	11	-15%
20	2040	1891	108%	2040	108%	1450	1450	0%	2730	2522	108%	2730	108%	1610	1610	0%	22	20	110%	22	110%	19	19	0%
22	2385	2179	109%	2385	109%	1840	1805	-2%	4580	4397	104%	4580	104%	3280	2850	-13%	28	27	104%	28	104%	21	20	-5%
24	1942	1785	109%	1942	109%	1490	1005	-33%	3375	3056	110%	3375	110%	2580	1470	-43%	26	27	96%	26	96%	14	9	-36%
25	3040	2913	104%	2890	99%	2200	2200	0%	4450	4090	109%	4270	104%	3210	3210	0%	31	32	97%	30	94%	17	17	0%
27	1660	1518	109%	1660	109%	1350	1350	0%	2605	2575	101%	2605	101%	1635	1635	0%	15	15	100%	15	100%	13	13	0%
28	3050	2891	105%	3050	105%	2520	1560	-38%	4670	4234	110%	4670	110%	4070	2300	-43%	35	36	97%	35	97%	23	13	-43%
Mean	2692	2545	106%	2602	103%	1966	1683	-14%	4038	3944	103%	3969	101%	2730	2295	-15%	23	22	103%	23	102%	15	13	-15%

Table 2B. Dietary variables of 21 women during follicular (F) and luteal (L) phase experiments.

	CARBOHYDRATES (g)								FAT (g)								PROTEIN (g)							
Subj. #	**prov**	**goal**	**prov/goal**	**24 hr**	**%eaten**	**con**	**alt**	**%diff**	**prov**	**goal**	**prov/goal**	**24 hr**	**%eaten**	**con**	**alt**	**%diff**	**prov**	**goal**	**prov/goal**	**24 hr**	**%eaten**	**con**	**alt**	**%diff**
2F	243	220	111%	239	109%	198	224	13%	24	25	94%	24	94%	18	18	0%	92	99	93%	90	91%	77	75	-3%
2L																								
4F	174	147	119%	174	119%	118	79	-33%	65	69	94%	65	94%	54	36	-33%	88	84	105%	88	105%	73	54	-26%
4L	174	147	119%	174	119%	118	50	-58%	65	69	94%	65	94%	54	32	-42%	88	84	105%	88	105%	73	38	-48%
6F	255	228	112%	255	112%	179	179	0%	41	39	104%	41	104%	35	35	0%	59	54	109%	59	109%	46	46	0%
6L	255	228	112%	255	112%	179	161	-10%	41	39	104%	41	104%	35	29	-17%	59	54	109%	59	109%	46	32	-30%
8F	255	264	96%	255	96%	179	95	-47%	41	52	78%	41	78%	35	17	-51%	59	65	91%	59	91%	46	19	-59%
8L	255	264	96%	255	96%	179	39	-78%	41	52	78%	41	78%	35	8	-77%	59	65	91%	59	91%	46	5	-89%
13F	281	252	112%	249	99%	215	184	-14%	65	70	93%	58	83%	51	52	2%	98	99	99%	80	81%	67	74	10%
13L	278	252	110%	278	110%	220	220	0%	65	70	93%	65	93%	51	51	0%	97	99	98%	97	98%	67	67	0%
16F	449	447	100%	308	69%	183	107	-42%	63	63	100%	52	82%	44	19	-57%	79	82	96%	43	52%	28	13	-54%
16L	426	447	95%	300	67%	205	179	-13%	64	63	101%	47	74%	44	41	-7%	79	82	96%	44	53%	31	29	-6%
18F	250	224	112%	250	112%	191	191	0%	89	83	107%	89	107%	61	61	0%	59	59	100%	59	100%	42	42	0%
18L	250	224	112%	250	112%	191	191	0%	89	83	107%	89	107%	61	61	0%	59	59	100%	59	100%	42	42	0%
21F	331	294	113%	291	99%	215	74	-66%	54	57	94%	48	83%	42	12	-71%	66	60	110%	57	95%	44	19	-57%
21L	331	294	113%	331	113%	255	186	-27%	54	57	94%	54	94%	48	38	-21%	66	60	110%	66	110%	53	46	-13%
29F	311	272	115%	311	115%	245	245	0%	105	109	96%	105	96%	63	63	0%	75	71	106%	75	106%	58	58	0%
29L	318	272	117%	241	89%	172	193	12%	105	109	96%	69	63%	27	43	59%	76	71	107%	64	90%	47	40	-15%
30F	341	308	111%	341	111%	248	208	-16%	78	78	100%	78	100%	50	44	-12%	59	56	105%	59	105%	42	33	-21%
30L	341	308	111%	341	111%	248	248	0%	78	78	100%	78	100%	50	50	0%	59	56	105%	59	105%	42	42	0%
31F																								
31L	224	205	109%	224	109%	166	166	0%	67	67	99%	67	99%	43	43	0%	63	62	101%	63	101%	43	43	0%
37F	355	316	112%	318	101%	268	205	-24%	84	80	105%	74	93%	60	40	-33%	85	82	103%	70	85%	64	42	-35%
37L	355	316	112%	271	86%	268	143	-47%	84	80	105%	57	71%	47	29	-38%	85	82	103%	61	74%	46	26	-45%
38F	394	353	112%	394	112%	304	99	-68%	49	45	109%	49	109%	33	8	-76%	125	118	106%	125	106%	87	21	-76%
38L	412	353	117%	412	117%	325	164	-49%	45	45	100%	45	100%	30	13	-57%	111	118	94%	111	94%	75	39	-48%
39F	295	269	110%	234	87%	216	65	-70%	76	80	95%	66	83%	42	6	-86%	54	49	110%	51	104%	31	9	-71%
39L	295	269	110%	129	48%	216	16	-93%	76	80	95%	52	65%	28	10	-64%	54	49	110%	30	62%	10	2	-80%
41F	368	338	109%	302	89%	276	166	-40%	88	94	94%	70	74%	68	43	-38%	77	71	108%	61	86%	55	32	-41%
41L																								
43F	289	305	95%	158	52%	117	167	42%	38	37	103%	59	159%	45	17	-62%	61	59	103%	59	99%	54	35	-35%
43L	289	305	95%	246	81%	183	160	-13%	38	37	103%	36	97%	20	12	-40%	61	59	103%	51	86%	37	21	-43%
44F	316	281	112%	254	90%	177	177	0%	59	57	104%	47	82%	26	26	0%	69	67	103%	45	67%	27	27	0%
44L	316	281	112%	224	80%	146	239	63%	59	57	104%	43	76%	22	38	71%	69	67	103%	49	73%	31	51	66%
45F	536	498	108%	372	75%	273	132	-52%	96	89	107%	74	83%	53	13	-75%	94	91	103%	60	66%	31	12	-61%
45L	536	498	108%	259	52%	159	180	13%	96	89	107%	62	69%	41	26	-37%	94	91	103%	80	88%	51	21	-59%
46F	294	253	116%	294	116%	217	177	-18%	66	65	102%	61	94%	41	40	-2%	91	87	105%	83	95%	65	64	-2%
46L	294	253	116%	294	116%	217	217	0%	66	65	102%	66	102%	46	46	0%	91	87	105%	91	105%	73	73	0%
11F	275	238	116%	260	109%	184	184	0%	51	56	91%	51	91%	41	41	0%	67	72	93%	65	90%	51	51	0%
11L																								
23F	324	297	109%	324	109%	252	252	0%	81	74	109%	81	109%	62	62	0%	53	48	110%	53	110%	39	39	0%
23L																								
Mean F	**317**	**290**	**110%**	**279**	**99%**	**213**	**160**	**-22%**	**66**	**66**	**99%**	**62**	**95%**	**46**	**33**	**-30%**	**75**	**74**	**103%**	**67**	**92%**	**51**	**38**	**-26%**
Mean L	**315**	**289**	**110%**	**264**	**95%**	**203**	**162**	**-18%**	**67**	**67**	**99%**	**57**	**87%**	**40**	**33**	**-16%**	**75**	**73**	**103%**	**66**	**91%**	**48**	**36**	**-24%**

Table 2B (cont'd) Dietary variables of 21 women during follicular (F) and luteal (L) phase experiments.

	CALORIES								SODIUM (mg)								FIBER (g)							
Subj. #	prov	goal	prov/goal	24 hr	%eaten	con	alt	%diff	prov	goal	prov/goal	24 hr	%eaten	con	alt	%diff	prov	goal	prov/goal	24 hr	%eaten	con	alt	%diff
2F	1553	1501	103%	1529	102%	1259	1354	8%	6027	6087	99%	5560	91%	4840	4404	-9%	16	15	107%	15	100%	12	11	-8%
2L																								
4F	1632	1543	106%	1632	106%	1252	859	-31%	3437	3521	98%	3437	98%	2067	1579	-24%	15	14	107%	15	107%	6	6	0%
4L	1632	1543	106%	1632	106%	1252	637	-49%	3437	3521	98%	3437	98%	2067	1307	-37%	15	14	107%	15	107%	6	1	-83%
6F	1619	1477	110%	1619	110%	1209	1209	0%	2114	2090	101%	2114	101%	1379	1379	0%	11	11	100%	11	100%	8	8	0%
6L	1619	1477	110%	1619	110%	1209	1029	-15%	2114	2090	101%	2114	101%	1379	1269	-8%	11	11	100%	11	100%	8	7	-13%
8F	1619	1784	91%	1619	91%	1209	609	-50%	2114	2546	83%	2114	83%	1379	359	-74%	11	13	85%	11	85%	8	6	-25%
8L	1619	1784	91%	1619	91%	1209	249	-79%	2114	2546	83%	2114	83%	1379	199	-86%	11	13	85%	11	85%	8	3	-63%
13F	2102	2034	103%	1837	90%	1557	1502	-4%	3810	3730	102%	3150	84%	2340	1940	-17%	15	16	94%	14	88%	12	7	-42%
13L	2087	2034	103%	2087	103%	1607	1607	0%	3854	3730	103%	3854	103%	2764	2764	0%	15	16	94%	15	94%	13	13	0%
16F	2680	2687	100%	1870	70%	1240	648	-48%	2885	2795	103%	2150	77%	1480	630	-57%	17	16	106%	9	56%	5	3	-50%
16L	2590	2687	96%	1800	67%	1340	1200	-10%	3025	2795	108%	1800	64%	1340	1200	-10%	15	16	93%	9	56%	6	5	-17%
18F	2035	1879	108%	2035	108%	1480	1480	0%	4500	4843	93%	4500	93%	3010	3010	0%	16	17	94%	16	94%	11	11	0%
18L	2035	1879	108%	2035	108%	1480	1480	0%	4500	4843	93%	4500	93%	3010	3010	0%	16	17	94%	16	94%	11	11	0%
21F	2070	1928	107%	1820	94%	1410	480	-66%	2375	2159	110%	2175	101%	1440	320	-78%	19	21	90%	15	71%	12	8	-33%
21L	2070	1928	107%	2070	107%	1660	1265	-24%	2375	2159	110%	2375	110%	1640	1350	-18%	19	21	90%	19	90%	16	16	0%
29F	2490	2351	106%	2490	106%	1780	1780	0%	3390	3445	98%	3390	98%	2020	2020	0%	26	26	100%	26	100%	22	22	0%
29L	2520	2351	107%	1840	78%	1120	1320	18%	3360	3445	98%	2630	76%	1240	1630	31%	27	26	104%	24	92%	19	20	5%
30F	2300	2157	107%	2300	107%	1610	1360	-16%	2680	2520	106%	2680	106%	1570	1370	-13%	26	27	96%	26	96%	20	20	0%
30L	2300	2157	107%	2300	107%	1610	1610	0%	2680	2520	106%	2640	105%	1570	1570	0%	26	27	96%	26	96%	20	20	0%
31F																								
31L	1745	1616	108%	1745	108%	1215	1215	0%	1670	1568	107%	1670	107%	955	955	0%	18	19	92%	18	92%	12	12	0%
37F	2515	2311	109%	2215	96%	1865	1345	-28%	4980	5201	96%	4300	83%	3290	2100	-36%	23	21	109%	18	85%	15	10	-33%
37L	2515	2311	109%	1840	80%	1540	935	-39%	4980	5201	96%	3710	71%	3030	1770	-42%	23	21	109%	18	83%	13	7	-44%
38F	2515	2290	110%	2515	110%	1860	550	-70%	4685	4329	108%	4685	108%	3165	265	-92%	18	17	108%	18	108%	14	4	-71%
38L	2495	2290	109%	2495	109%	1870	930	-50%	4540	4329	105%	4540	105%	3060	1630	-47%	24	17	144%	24	144%	18	8	-56%
39F	2081	1990	105%	1735	87%	1120	350	-69%	3404	3334	102%	2780	83%	1520	220	-86%	20	21	95%	18	86%	11	4	-64%
39L	2081	1990	105%	1105	56%	490	160	-67%	3404	3334	102%	1828	55%	568	180	-68%	20	21	95%	10	46%	3	1	-64%
41F	2570	2480	104%	2082	84%	1935	1175	-39%	4560	4468	102%	3727	83%	3405	1530	-55%	30	30	100%	24	80%	17	8	-53%
41L																								
43F	1740	1787	97%	1397	78%	1087	960	-12%	3395	3296	103%	2616	79%	2196	1390	-37%	32	29	110%	18	62%	16	15	-9%
43L	1740	1787	97%	1510	84%	1060	830	-22%	3395	3296	103%	2645	80%	1475	1195	-19%	32	29	110%	25	86%	16	16	0%
44F	2070	1905	109%	1620	85%	1050	1050	0%	2450	2575	95%	2060	80%	1250	1210	-3%	19	18	106%	18	100%	14	14	0%
44L	2070	1905	109%	1478	78%	908	1500	65%	2450	2575	95%	1996	78%	1186	1640	38%	19	18	106%	19	104%	15	15	2%
45F	3384	3161	107%	2394	76%	1692	693	-59%	4124	4202	98%	3334	79%	2252	913	-59%	19	18	106%	12	67%	7	4	-43%
45L	3384	3161	107%	1912	60%	1210	1035	-14%	4124	4202	98%	2902	69%	1820	1369	-25%	19	18	106%	15	83%	10	7	-30%
46F	2135	1944	110%	2055	106%	1495	1325	-11%	3930	3843	102%	3750	98%	2090	2070	-1%	22	22	100%	22	100%	16	16	0%
46L	2135	1944	110%	2135	110%	1575	1575	0%	3930	3843	102%	3930	102%	2270	2270	0%	22	22	100%	22	100%	16	16	0%
11F	1827	1743	105%	1757	101%	1307	1307	0%	3405	3730	91%	2545	68%	1615	1615	0%	15	15	100%	13	87%	10	10	0%
11L																								
23F	2235	2047	109%	2235	109%	1720	1720	0%	3260	3614	90%	3260	90%	1850	1850	0%	10	10	100%	10	100%	7	7	0%
23L																								
Mean F	**2159**	**2050**	**105%**	**1938**	**96%**	**1457**	**1088**	**-25%**	**3576**	**3616**	**99%**	**3216**	**89%**	**2208**	**1509**	**-32%**	**19**	**19**	**101%**	**16**	**89%**	**12**	**10**	**-22%**
Mean L	**2155**	**2050**	**105%**	**1837**	**92%**	**1315**	**1093**	**-17%**	**3291**	**3294**	**100%**	**2864**	**88%**	**1809**	**1489**	**-17%**	**20**	**19**	**101%**	**17**	**91%**	**12**	**10**	**-21%**

Table 2C. Dietary variables of 21 women on oral contraceptives for experiments during placebo (C) and pill (P) week.

	CARBOHYDRATES (g)								FAT (g)								PROTEIN (g)							
Subj. #	**prov**	**goal**	**prov/goal**	**24 hr**	**%eaten**	**con**	**alt**	**%diff**	**prov**	**goal**	**prov/goal**	**24 hr**	**%eaten**	**con**	**alt**	**%diff**	**prov**	**goal**	**prov/goal**	**24 hr**	**%eaten**	**con**	**alt**	**%diff**
4C	186	147	127%	184	126%	129	72	-45%	66	69	96%	56	81%	45	15	-66%	91	84	108%	75	89%	65	17	-74%
4P	186	147	127%	186	127%	97	47	-51%	66	69	96%	66	96%	46	18	-60%	91	84	108%	91	108%	72	27	-63%
6C	255	228	112%	255	112%	167	167	0%	44	39	113%	44	113%	37	37	0%	59	54	108%	59	108%	45	45	0%
6P	248	228	109%	248	109%	167	167	0%	43	39	110%	43	110%	37	37	0%	58	54	106%	58	106%	45	45	0%
16C	199	167	119%	125	75%	87	63	-27%	56	55	101%	41	75%	25	20	-21%	68	68	100%	50	74%	36	14	-62%
16P	199	167	119%	199	119%	160	82	-49%	56	55	101%	56	101%	40	19	-52%	68	68	100%	68	100%	54	15	-72%
21C	352	294	120%	22	7%	22	0	-100%	50	57	88%	0	0%	0	0	0%	71	60	118%	1	2%	1	0	-100%
21P	331	294	113%	242	82%	202	0	-100%	54	57	94%	38	66%	38	0	-100%	66	60	110%	33	55%	33	0	-100%
29C	318	272	117%	249	92%	249	188	-25%	105	109	96%	63	58%	63	51	-19%	76	71	107%	59	83%	59	35	-41%
29P	314	272	116%	314	116%	245	245	0%	105	109	96%	105	96%	63	63	0%	75	71	106%	75	106%	58	58	0%
32C																								
32P	432	428	101%	392	92%	277	282	2%	79	72	110%	73	101%	51	51	0%	98	96	102%	89	93%	73	73	0%
33C	309	293	106%	309	106%	211	211	0%	78	82	95%	78	95%	45	45	0%	89	85	105%	89	105%	68	68	0%
33P	309	293	106%	309	106%	211	149	-29%	78	82	95%	78	95%	45	33	-27%	89	85	105%	89	105%	68	44	-35%
34C	443	382	116%	443	116%	336	153	-55%	110	107	103%	110	103%	68	10	-85%	103	95	108%	103	108%	72	25	-65%
34P	460	382	120%	403	105%	309	215	-30%	96	107	90%	82	77%	44	37	-15%	104	95	109%	100	105%	65	44	-33%
35C	275	231	119%	275	119%	219	219	0%	70	73	96%	70	96%	50	50	0%	49	46	107%	49	107%	35	35	0%
35P	275	231	119%	275	119%	219	174	-21%	70	73	96%	70	96%	50	31	-38%	49	46	107%	49	107%	35	33	-6%
36C	330	299	110%	330	110%	265	222	-16%	64	59	108%	64	108%	54	37	-31%	94	104	90%	94	90%	79	60	-24%
36P	322	299	108%	270	90%	229	163	-29%	63	59	106%	49	83%	42	33	-21%	94	104	90%	63	61%	49	38	-22%
37C	358	316	113%	110	35%	110	158	44%	75	80	94%	38	48%	38	34	-11%	78	82	95%	30	37%	30	33	10%
37P	354	316	112%	186	59%	111	169	53%	75	80	94%	61	76%	36	42	17%	80	82	98%	52	63%	31	34	10%
38C	394	353	112%	334	95%	244	170	-30%	49	45	109%	43	96%	27	5	-83%	125	118	106%	109	92%	71	20	-72%
38P	349	353	99%	268	76%	243	95	-61%	44	45	98%	30	67%	23	9	-63%	111	118	94%	80	68%	63	23	-63%
40C	403	355	113%	403	113%	321	321	0%	52	50	104%	52	104%	38	38	0%	63	64	99%	63	99%	41	41	0%
40P	403	355	114%	360	101%	297	319	7%	53	50	106%	50	100%	41	41	0%	63	64	99%	58	91%	43	44	2%
42C	411	362	114%	411	114%	326	181	-45%	61	62	98%	61	98%	43	25	-42%	84	84	100%	84	100%	67	33	-51%
42P	411	362	114%	411	114%	326	63	-81%	61	62	98%	61	98%	43	14	-67%	84	84	100%	84	100%	67	16	-76%
44C	316	281	112%	316	112%	239	60	-75%	59	57	104%	59	104%	38	14	-63%	69	67	103%	69	103%	51	14	-73%
44P	316	281	112%	242	86%	165	99	-40%	59	57	104%	47	82%	26	17	-35%	69	67	103%	45	67%	27	8	-70%
45C	390	498	78%	162	32%	119	3	-97%	78	89	87%	43	48%	36	2	-95%	87	91	96%	24	26%	10	0	-95%
45P	536	498	108%	224	45%	224	158	-29%	96	89	107%	77	86%	56	24	-57%	94	91	103%	65	71%	36	21	-41%
47C	240	219	110%	219	100%	147	134	-9%	54	53	102%	48	91%	42	34	-19%	62	62	100%	47	76%	35	46	31%
47P	240	219	110%	199	91%	127	134	6%	54	53	102%	42	79%	36	34	-6%	62	62	100%	33	53%	21	46	119%
48C	326	283	115%	300	106%	235	132	-44%	50	49	102%	47	96%	38	28	-26%	69	71	97%	67	94%	55	33	-40%
48P	326	283	115%	326	115%	148	144	-3%	50	49	102%	44	90%	32	15	-53%	69	71	97%	47	66%	33	28	-17%
49C	278	281	99%	278	99%	232	149	-36%	86	80	108%	86	108%	71	51	-28%	84	83	101%	84	101%	60	41	-32%
49P	293	281	104%	293	104%	242	242	0%	80	80	100%	80	100%	68	68	0%	82	83	99%	82	99%	59	59	0%
50C	250	262	95%	250	95%	250	194	-23%	70	38	184%	70	184%	70	43	-39%	45	99	45%	45	45%	45	27	-40%
50P	239	262	91%	239	91%	140	140	0%	48	38	126%	48	126%	27	27	0%	54	99	55%	54	55%	25	25	0%
26C																								
26P	274	264	104%	274	104%	191	191	0%	43	43	99%	43	99%	37	37	0%	60	58	103%	60	103%	46	46	0%
Mean C	**317**	**291**	**111%**	**262**	**93%**	**205**	**147**	**-31%**	**67**	**66**	**105%**	**56**	**90%**	**44**	**28**	**-33%**	**77**	**78**	**100%**	**63**	**81%**	**49**	**31**	**-38%**
Mean P	**325**	**296**	**110%**	**279**	**98%**	**206**	**156**	**-22%**	**65**	**65**	**101%**	**59**	**92%**	**42**	**31**	**-28%**	**77**	**78**	**100%**	**65**	**85%**	**48**	**35**	**-22%**

Table 2C (cont'd). Dietary variables of 21 women on oral contraceptives for experiments during placebo (C) and pill (P) week.

	CALORIES								SODIUM (mg)								FIBER (g)							
Subj. #	prov	goal	prov/goal	24 hr	%eaten	con	alt	%diff	prov	goal	prov/goal	24 hr	%eaten	con	alt	%diff	prov	goal	prov/goal	24 hr	%eaten	con	alt	%diff
4C	1702	1543	110%	1542	100%	1182	492	-58%	3747	3521	106%	3387	96%	1997	1067	-47%	15	14	107%	15	107%	6	5	-17%
4P	1702	1543	110%	1702	110%	1092	462	-58%	3747	3521	106%	3747	106%	2157	947	-56%	15	14	107%	15	107%	6	5	-17%
6C	1649	1477	112%	1649	112%	1179	1179	0%	1934	2090	93%	1934	93%	1294	1294	0%	12	11	105%	12	105%	9	9	0%
6P	1609	1477	109%	1609	109%	1179	1179	0%	2014	2090	96%	2014	96%	1274	1274	0%	11	11	95%	11	95%	8	8	0%
16C	1570	1435	109%	1070	75%	715	485	-32%	2920	3089	95%	2520	82%	1100	920	-16%	16	16	100%	12	75%	8	2	-75%
16P	1570	1435	109%	1570	109%	1215	560	-54%	2920	3089	95%	2920	95%	1500	570	-62%	16	16	100%	16	100%	12	7	-42%
21C	2140	1928	111%	90	5%	90	0	-100%	2425	2159	112%	0	0%	0	0	0%	21	21	100%	2	10%	2	0	-100%
21P	2070	1928	107%	1438	75%	1278	0	-100%	2375	2159	110%	1405	65%	1370	0	-100%	19	21	90%	12	57%	12	0	-100%
29C	2520	2351	107%	1800	77%	1800	1350	-25%	3360	3445	98%	1970	57%	1970	1580	-20%	27	26	104%	22	85%	22	21	-5%
29P	2500	2351	106%	2500	106%	1780	1780	0%	3410	3445	99%	3410	99%	2020	2020	0%	27	26	104%	27	104%	22	22	0%
32C																								
32P	2830	2742	103%	2580	94%	1860	1880	1%	3235	3222	100%	3035	94%	1980	1980	0%	24	24	100%	24	100%	20	20	0%
33C	2295	2248	102%	2295	102%	1520	1520	0%	3700	3638	102%	3700	102%	2100	2100	0%	17	17	100%	17	100%	11	11	0%
33P	2295	2248	102%	2295	102%	1520	1070	-30%	3700	3638	102%	3700	102%	2100	1710	-19%	17	17	100%	17	100%	11	10	-9%
34C	3174	2874	110%	3174	110%	2242	800	-64%	4384	4646	94%	4384	94%	2842	365	-87%	19	21	92%	19	92%	13	6	-54%
34P	3120	2874	109%	2750	96%	1890	1370	-28%	4455	4646	96%	4135	89%	2990	2015	-33%	22	21	107%	22	107%	13	10	-27%
35C	1926	1763	109%	1926	109%	1465	1465	0%	3410	3588	95%	3410	95%	1844	1844	0%	8	8	100%	8	100%	4	4	0%
35P	1926	1763	109%	1926	109%	1465	1106	-25%	3410	3588	95%	3410	95%	1844	1425	-23%	8	8	100%	8	100%	4	3	-25%
36C	2271	2144	106%	2271	106%	1861	1461	-21%	3395	3195	106%	3395	106%	2365	1885	-20%	18	18	100%	18	100%	14	12	-14%
36P	2226	2144	104%	1771	83%	1491	1101	-26%	3508	3195	110%	3065	96%	2145	1835	-14%	19	18	103%	16	89%	13	8	-38%
37C	2420	2311	105%	900	39%	900	1070	19%	5460	5201	105%	2985	57%	2985	2175	-27%	21	21	99%	7	33%	7	7	0%
37P	2410	2311	104%	1500	65%	890	1190	34%	5270	5201	101%	3890	75%	2830	1510	-47%	21	21	99%	14	66%	7	6	-14%
38C	2515	2290	110%	2155	94%	1500	800	-47%	4685	4329	108%	3025	70%	1505	1200	-20%	18	17	108%	14	81%	10	6	-42%
38P	2235	2290	98%	1660	72%	1430	550	-62%	3665	4329	85%	1335	31%	1105	495	-55%	16	17	96%	10	60%	10	4	-65%
40C	2330	2122	110%	2330	110%	1790	1790	0%	2775	2619	106%	2775	106%	1770	1770	0%	19	20	95%	19	95%	14	14	0%
40P	2340	2122	110%	2120	100%	1730	1820	5%	2560	2619	98%	2470	94%	1660	1685	2%	20	20	101%	19	95%	15	15	0%
42C	2530	2343	108%	2530	108%	1960	1080	-45%	3960	4140	96%	3960	96%	2870	2230	-22%	14	14	100%	14	100%	9	5	-44%
42P	2530	2343	108%	2530	108%	1960	443	-77%	3960	4140	96%	3960	96%	2870	1170	-59%	14	14	100%	14	100%	9	3	-67%
44C	2070	1905	109%	2070	109%	1500	420	-72%	2450	2575	95%	2450	95%	1640	810	-51%	19	18	106%	19	106%	15	12	-20%
44P	2070	1905	109%	1570	82%	1000	580	-42%	2450	2575	95%	2050	80%	1240	530	-57%	19	18	106%	18	100%	14	3	-79%
45C	2610	3161	83%	1130	36%	840	32	-96%	3030	4202	72%	1450	35%	840	53	-94%	16	18	89%	4	22%	1	0	-100%
45P	3384	3161	107%	2245	71%	1543	933	-40%	4134	4202	98%	3405	81%	2313	1333	-42%	19	18	106%	12	67%	7	7	0%
47C	1695	1601	106%	1495	93%	1105	1025	-7%	2020	1853	109%	1830	99%	1150	1190	3%	13	12	108%	11	92%	7	8	14%
47P	1695	1601	106%	1305	82%	915	1025	12%	2020	1853	109%	1680	91%	1000	1190	19%	13	12	108%	8	67%	4	8	100%
48C	2030	1856	109%	1890	102%	1500	910	-39%	3190	3083	103%	3080	100%	2380	860	-64%	17	17	100%	16	94%	12	5	-58%
48P	2030	1856	109%	1540	83%	1010	820	-19%	3190	3083	103%	2160	70%	1350	1315	-3%	17	17	100%	13	76%	8	5	-38%
49C	2220	2188	101%	2220	101%	1805	1220	-32%	4040	3782	107%	4040	107%	2750	1500	-45%	14	13	108%	14	108%	8	5	-38%
49P	2220	2188	101%	2220	101%	1815	1815	0%	3880	3782	103%	3880	103%	2670	2670	0%	12	13	92%	12	92%	8	8	0%
50C	1810	1786	101%	1810	101%	1810	1270	-30%	3080	4195	73%	3080	73%	3080	1550	-50%	11	21	52%	11	52%	11	7	-36%
50P	1604	1786	90%	1604	90%	902	902	0%	2414	4195	58%	2414	58%	1332	1332	0%	17	21	81%	17	81%	12	12	0%
26C																								
26P	1720	1668	103%	1720	103%	1280	1280	0%	2820	2660	106%	2820	106%	2250	2250	0%	27	26	104%	27	104%	15	15	0%
Mean C	**2183**	**2070**	**106%**	**1808**	**89%**	**1409**	**967**	**-34%**	**3367**	**3440**	**99%**	**2809**	**82%**	**1920**	**1284**	**-29%**	**17**	**17**	**99%**	**13**	**82%**	**10**	**7**	**-31%**
Mean P	**2195**	**2083**	**105%**	**1912**	**93%**	**1393**	**1041**	**-24%**	**3292**	**3392**	**98%**	**2900**	**87%**	**1905**	**1393**	**-26%**	**18**	**18**	**100%**	**16**	**89%**	**11**	**8**	**-20%**

Table 3. Responses of norepinephrine, epinephrine, pain, HR and MBP to 5 min coldpressor test in subject subgroups.

Men

Subj.#	AMSa	Norepi	Epi	Pain	HR	MBP
0	7.77	67	9	9	10	20
1	6.30	97	-3	8	75	63
3	0.76	-97	-5	5	18	31
5	7.61	122	0	4	2	4
7	3.12	20	45	7	13	28
9	5.77	575	112	10	16	18
10	9.83	-220	49	6	30	26
12	3.93	126	2	4	25	18
14	1.18	72	-2	5	21	17
15	1.26	225	18	3	17	26
17	1.79	375	9	3	29	21
19	0.94	510	22	7	0	13
20	1.40	-105	-25	6	19	35
22	4.42	103	3	10	16	54
24	5.35	328	39	4	11	48
25	7.74	638	9	8	4	53
27	0.67	752	-24	4	7	32
28	5.26	717	-41	9	34	34
Mean	4.17	239	12	6.2	19	30

Follicular

Subj.#	AMSa	Norepi	Epi	Pain	HR	MBP
4	2.11	-95	173	9	22	6
6	2.40	55	0	10	17	30
16	4.98	40	4	8	6	21
21	3.65	-102	0	4	10	20
29	1.40	146	53	4	3	5
37	4.57	120	49	3	24	23
38	10.18	-109	-34	1	59	17
44	8.37	176	-123	4	6	13
45	9.70	196	80	8	2	17
2	2.51	34	0	8	13	11
8	5.92	65	-6	7	21	16
13	1.15	-53	-16	9	21	18
18	0.58	811	27	10	30	36
30	4.31	-126	438	4	-2	14
31	2.11	514	0	7	-24	14
39	7.22	134	104	10	1	25
41	3.20	-196	71	6	5	17
43	2.66	38	11	6	2	28
46	3.61	582	-108	8	51	46
11	4.00	518	8	8	24	47
23	6.63	-26	-44	4	14	22
Mean	4.35	130	33	6.6	15	21

Luteal

Subj.#	AMSa	Norepi	Epi	Pain	HR	MBP
4	3.53	151	40	8	-13	44
6	1.19	78	-7	10	27	25
16	4.09	152	25	9	11	13
21	4.98	266	-26	6	7	20
29	1.19	314	34	5	-11	21
37	3.98	352	52	3	12	20
38	4.54	75	-22	2	24	26
44	3.59	106	12	2	0	20
45	5.14	245	61	7	24	23
2	0.70	65	4		19	18
8	5.00	-191	2	7	20	13
13	1.25	134	-14	7	10	25
18	3.72	305	6	8	28	23
30	2.61	47	382	5	13	16
31	6.45	402		8	6	26
39	4.57	179	-8	9	7	17
41	7.82	-61	1	6	6	16
43	3.04	222	21	5	6	11
46	2.34	668	119	8	37	38
Mean	3.67	185	38	6.4	12	22

Placebo

Subj.#	AMSa	Norepi	Epi	Pain	HR	MBP
4	3.41	29	7	10	14	16
6	2.32	199	-19	10	5	26
16	5.81	74	4	8	15	1
21	4.85	252	26	5	14	26
29	2.05	4	201	5	4	22
37	3.59	326	-342	3	7	24
38	3.65	-111	8	3	15	30
44	5.64	118	-2	4	-1	15
45	5.69	163	-2	8	16	30
32	1.89	195	3	7	70	33
33	1.08	-2		3	-1	20
34	7.85	139	-138	9	23	24
35	2.25	-7	51	9	14	29
36	5.24	6	-328	4	13	18
40	2.61	-21	26	8	19	17
42	8.52	121	-1045	6	-7	13
47	6.38	2672	-123	9	24	19
48	7.29	130	-55	6	13	26
49	3.20	412	278	7	53	26
50	1.40	459	27	7	18	32
Mean	4.24	258	-75	6.6	16	22

Pill

Subj.#	AMSa	Norepi	Epi	Pain	HR	MBP
4	3.59	83	0	8	16	27
6	1.19	152	138	10	17	34
16	3.55	74	4	8	15	1
21	5.74	165	-32	5	16	26
29	0.89	-118	-2666	3	11	20
37	5.47	3030	286	3	20	15
38	3.40	-179	0	4	17	24
44	5.77	124	-32	3	13	8
45	8.00	225	-3	7	13	15
32	3.75	250	247	6	3	19
33	4.97	20	261	2	14	14
34	3.62	123	51	8	20	32
35	4.38	-137	136	9	32	8
36	3.78	20	90	4	19	28
40	5.19	-23	186	8	34	5
42	7.91	60	4	4	5	18
47	5.80	-776	-61	10	35	2
48	7.27	-1	21	7	15	23
49	3.54	-177	99	7	21	14
50	0.88	-131	-35	6	18	35
26	5.74	321	8	8	-6	11
Mean	4.50	148	-62	6.2	17	18

Table 4: Statistical comparison of responses to CPT for all subgroups.

ΔNorepi

	Group Total			9 Common Group Paired-t \ **PROB** \ ANOVA				All-paired			vs. AMS_a		
	n	Mean	SD	Foll	Lut	C	Pill	n	Mean	SD	n	r	P
Men	18	239	295	0.23	0.50	0.90	0.61				18	-0.10	0.69
Foll	21	130	265		0.46	0.37	0.91	19	117	261	21	-0.22	0.34
								P=0.16					
Lut	19	185	186	**0.011**		0.61	0.83	19	185	186	19	-0.14	0.57
C (plac)	20	258	587	0.21	0.10		0.59	20	258	587	20	0.21	0.38
								P=0.61					
Pill	21	148	698	0.31	0.54	0.39		20	139	715	21	0.14	0.54

ΔEpi

	Group Total			9 Common Group Paired-t \ **PROB** \ ANOVA				All-paired			vs. AMS_a		
	n	Mean	SD	Foll	Lut	C	Pill	n	Mean	SD	n	r	P
Men	18	12	34	0.46	0.28	0.19	0.61				18	0.29	0.24
Foll	21	33	114		0.88	0.11	0.49	18	40	121	21	-0.11	0.63
								P=0.91					
Lut	18	38	93	0.88		0.11	0.49	18	38	93	18	-0.16	0.52
C (plac)	19	-75	276	0.53	0.54		0.93	19	-75	276	19	-0.58	**0.010**
								P=0.97					
Pill	21	-62	606	0.39	0.39	0.49		19	-82	633	21	0.38	0.09

Δpain

	Group Total			9 Common Group Paired-t \ **PROB** \ ANOVA				All-paired			vs. AMS_a		
	n	Mean	SD	Foll	Lut	C	Pill	n	Mean	SD	n	r	P
Men	18	6.2	2.4	0.67	0.83	0.67	0.97				18	0.42	0.08
Foll	21	6.6	2.6		0.82	0.98	0.63	18	6.6	2.7	21	-0.40	0.07
								P=0.56					
Lut	18	6.4	2.4	0.80		0.83	0.80	18	6.4	2.4	18	-0.06	0.83
C (plac)	20	6.6	2.4	0.05	0.27		0.63	20	6.6	2.4	20	0.07	0.77
								P=0.046					
Pill	21	6	2.4	1.00	0.78	0.14		20	6.1	2.5	21	-0.07	0.09

ΔHR

	Group Total			9 Common Group Paired-t \ **PROB** \ ANOVA				All-paired			vs. AMS_a		
	n	Mean	SD	Foll	Lut	C	Pill	n	Mean	SD	n	r	P
Men	18	19	17	0.40	0.16	0.61	0.53				18	0.15	0.55
Foll	21	15	18		0.65	0.74	0.65	19	14	19	21	0.15	0.50
								P=0.64					
Lut	19	12	13	0.27		0.41	0.23	19	12	13	19	-0.08	0.74
C (plac)	20	16	18	0.28	0.86		0.97	20	16	18	20	-0.21	0.37
								P=0.77					
Pill	21	17	10	0.83	0.21	**0.031**		20	18	8	21	-0.10	0.68

ΔMBP

	Group Total			9 Common Group Paired-t \ **PROB** \ ANOVA				All-paired			vs. AMS_a		
	n	Mean	SD	Foll	Lut	C	Pill	n	Mean	SD	n	r	P
Men	18	30	16	**0.049**	0.05	0.06	**0.007**				18	0.16	0.53
Foll	21	21	11		0.85	0.71	0.34	19	20	10	21	-0.09	0.70
								P=0.49					
Lut	19	22	8	0.19		0.85	0.2	19	22	8	19	-0.16	0.52
C (plac)	20	22	8	0.3	0.53		0.14	20	22	8	20	-0.38	0.10
								P=0.08					
Pill	21	18	10	0.64	0.14	0.44		20	18	10	21	-0.43	0.05

Table 5A. Resting ventilation (L/min) of 18 men.

Subj. #	C12	A1	A6	A12	Δ%
0	10.5	13.7	11.6	10.4	13
1	5.1		8.1	9.9	76
3	8.0	14.3	16.1	17.6	101
5	8.2	10.4	10.6	10.7	29
7	7.4	11.1	11.5	9.3	45
9	9.4	12.8	13.2	13.1	39
10	9.2	11.4	12.3	14.9	40
12	9.4	10.3	10.7	12.8	21
14	7.8	10.7	10.8	9.6	33
15	8.4	11.7	13.9	16.1	66
17	7.5	8.8	9.2	8.5	18
19	8.3	7.8	11.3	7.4	7
20	7.2	9.2	9.1	8.2	22
22	8.5	10.6	13.7	10.3	36
24	7.4	8.1	6.9	7.1	-1
25	6.8	9.7	11.1	8.5	43
27	7.7	8.1	10.5	10.8	28
28	8.3	10.8	11.6	11.3	35
Mean	**8.0**	**10.5**	**11.2**	**10.9**	**36**

C12: Ventilation on control day

A1, A6, A12: Ventilation at hour 1, 6 and 12 (or last hr) at altitude.

Δ%: Percent change of A1-A6-A12 average from C12

Table 5B. Resting ventilation (L/min) of 21 women during follicular (F) and luteal (L) experiments.

Subj. #	C12	A1	A6	A12	Δ%
2F	9.2	12.0	12.9	12.1	34
2L	10.5	10.0	7.9	9.3	-13
4F	10.0	7.8	6.1	6.5	-32
4L	6.7	9.3	9.1	7.8	30
6F	7.1	7.6	6.7	8.7	7
6L	7.2	8.2	8.4	8.0	14
8F	7.3	8.0	9.6	9.6	23
8L	7.9	14.0	10.3	10.3	45
13F	8.1	7.1	9.1	8.0	0
13L	9.1	9.3	13.3	9.3	16
16F	5.5	7.4	6.2	7.3	26
16L	6.0	7.1	6.9	9.6	31
18F	5.9	7.8	11.0	9.3	58
18L	7.1	8.1	11.7	7.2	26
21F	8.2	7.9	8.3	9.1	2
21L	5.3	9.9	9.9	9.9	87
29F	9.4	8.8	8.8	8.1	-9
29L	6.5	8.5	9.1	8.0	31
30F	7.1	8.6	8.9	9.2	25
30L	7.2	10.0	10.3	8.4	33
31F	6.5	7.4	8.5	7.9	22
31L	7.1	9.0	8.7	9.5	29
37F	5.6	9.1	9.8	13.8	94
37L	7.5	10.8	13.5	10.4	54
38F	5.6	6.0	7.8	7.1	25
38L	5.8	6.4	7.1	8.6	27
39F	7.3	7.8	9.9	9.9	26
39L	8.5	8.2	8.9	8.9	1
41F	6.8	8.2	9.7	8.1	26
41L	6.6	9.4	9.6	9.4	44
43F	7.5	8.2	8.8	8.9	15
43L	8.2	9.3	10.5	10.0	20
44F	7.2	7.9	7.5	7.5	6
44L	8.7	9.5	9.6	10.4	13
45F	8.8	9.2	7.9	9.6	1
45L	6.7	8.1	7.6	8.4	20
46F	6.2	9.8	9.0	10.5	58
46L	5.1	8.2	12.5	8.8	93
11F	5.0	6.7	7.8	8.4	51
11L					
23F	5.6	7.8	7.2	6.0	26
23L					
Mean F	**7.2**	**8.1**	**8.6**	**8.8**	**23**
Mean L	**7.2**	**9.1**	**9.7**	**9.1**	**32**

C12: Ventilation on control day

A1, A6, A12: Ventilation at hour 1, 6 and 12 (or last hr) at altitude

Δ%: Percent change of A1-A6-A12 average from C12

Table 5C. Resting ventilation (L/min) of 21 women on oral contraceptives during placebo (C) and pill (P) experiments.

Subj. #	C12	A1	A6	A12	Δ%
4C	6.7	6.9	8.7	8.2	18
4P	6.9	6.9	8.4	8.9	16
6C	10.1	8.4	10.0	8.5	-11
6P	8.3	8.8	9.4	8.4	6
16C	6.4	7.5	8.7	7.3	22
16P	6.4	6.7	7.8	7.0	12
21C	6.3	8.1	9.0	8.1	33
21P	9.2	8.6	8.9	10.4	1
29C	7.1	9.1	9.3	8.1	24
29P	7.4	9.3	10.0	8.9	28
32C	6.7	8.6	9.8	8.2	33
32P	7.8	8.6	6.5	7.9	-1
33C	7.3	8.8	9.7	10.6	33
33P	6.6	13.4	11.4	11.8	86
34C	7.7				
34P	7.8	8.8	9.8	9.5	20
35C	5.8	7.3	7.5	6.3	21
35P	7.3	8.5	9.4	7.0	13
36C	8.3	10.0	10.0	9.9	20
36P	8.3	10.6	10.9	9.8	27
37C	7.7	12.1	10.1	10.2	39
37P	8.9	9.4	13.2	11.8	29
38C	6.2	6.3	7.1	6.4	7
38P	6.9	7.3	7.1	10.4	19
40C	5.7	7.4	7.5	8.3	37
40P	6.0	7.8	7.1		24
42C	6.0	6.6	8.2	8.9	32
42P	7.8	6.9	7.5	8.6	-2
44C	7.3	7.9	9.5	9.3	21
44P	7.7	8.9	10.3	9.8	25
45C	7.3	7.5	8.4	10.0	18
45P	6.4	8.0	9.1	9.9	41
47C	5.9	8.4	7.3	8.2	36
47P	7.4	8.4	10.1	8.6	21
48C	9.4	11.5	9.9	11.6	18
48P	8.3	10.1	11.8	13.0	40
49C	6.1	6.7	7.2	6.6	12
49P	6.8		7.3	8.1	12
50C	5.5			7.0	28
50P	7.7	7.4	7.3	8.7	2
26C					
26P	8.5	8.1	16.0	14.3	51
Mean C	**7.0**	**8.3**	**8.8**	**8.5**	**23**
Mean P	**7.5**	**8.6**	**9.5**	**9.6**	**22**

C12: Ventilation on control day

A1, A6, A12: Ventilation at hour 1, 6 and 12 or last hr) at altitude

Δ%: Percent change of A1-A6-A12 average from C12

Table 6. Average responses to 3-breath tests of N_2 and O_2 by subjects in 5 subgroups.

		N_2 test					O_2 test				
		C12	**A1**	**A6**	**A12**	**Aav**	**C12**	**A1**	**A6**	**A12**	**Aav**
	n	17	17	17	17	18	17	16	16	15	18
Men	Mean	**35**	**42**	**37**	**42**	**41**	**3**	**-28**	**-18**	**-14**	**-20**
	SD	49	28	31	33	28	33	18	16	16	14
	n	21	20	19	17	20	21	19	19	17	21
Fol	Mean	**30**	**45**	**56**	**48**	**49**	**-8**	**-27**	**-20**	**-17**	**-22**
	SD	23	30	39	45	32	13	18	23	19	16
	n	19	19	19	17	19	19	16	17	16	19
Lut	Mean	**30**	**39**	**40**	**45**	**41**	**-9**	**-25**	**-22**	**-16**	**-21**
	SD	22	32	36	32	27	13	17	18	18	14
	n	18	18	12	17	19	18	17	13	17	19
Pla	Mean	**26**	**37**	**42**	**37**	**41**	**-10**	**-13**	**-25**	**-26**	**-20**
	SD	29	26	28	47	34	11	39	15	13	19
	n	21	20	18	19	21	21	17	16	19	21
Pil	Mean	**26**	**33**	**41**	**31**	**37**	**-5**	**-21**	**-29**	**-11**	**-21**
	SD	21	24	35	27	26	13	26	22	31	17
	n	96	94	85	87	97	96	85	81	84	98
All	Mean	**29**	**39**	**43**	**41**	**42**	**-6**	**-23**	**-23**	**-17**	**-21**
	SD	29	28	35	37	29	18	25	19	21	16

Aav: average value at A1, A6 and A12 at altitude

Table 7A. Arterial blood gas values of 18 men during the 2nd and 12th hr (A1, A12) at altitude.

	C12		A1			A12			A12-A1	
Subj. #	pHa	P_aCO_2	pHa	P_aO_2	P_aCO_2	pHa	P_aO_2	P_aCO_2	ΔPO_2	ΔPCO_2
0			7.450	48.4	36.1	7.496	52.7	28.3	-2.8	-9.7
1	7.455	36.5				7.520	47.0	26.0		
3	7.393	35.7	7.420	51.3	32.0	7.440	52.5	30.0	1.9	-1.4
5	7.395	36.0	7.415	49.0	31.5	7.435	47.5	29.5	1.2	1.3
7	7.390	41.0	7.435	47.0	36.5	7.450	42.5	33.5	2.7	-1.7
9	7.400	39.5	7.410	42.0	40.0	7.455	38.5	34.5	4.7	-2
10	7.413	40.4	7.432	41.3	38.4	7.459	40.8	31.6	5.8	-1.1
12	7.429	36.6	7.443	43.3	34.1	7.479	48.7	28.5	-0.5	0.2
14	7.420	42.8	7.435	41.2	38.2	7.465	38.2	33.4	2.2	-2.2
15	7.428	37.6	7.471	47.2	32.8	7.445	45.0	33.1	2.2	1.1
17	7.413	42.0	7.446	44.3	39.0	7.467	43.3	33.1	0.8	-2.3
19	7.445	36.1	7.466	42.9	32.5	7.466	41.2	31.1	1.2	-0.1
20	7.483	32.5	7.461	52.2	35.7	7.506	42.9	28.2	5.3	1.1
22	7.414	39.8	7.444	43.2	36.6	7.458	42.4	32.5	2.5	-0.6
24	7.419	41.6	7.472	35.9	36.0	7.469	35.4	33.1	0.7	-0.8
25	7.402	41.1	7.456	39.1	36.3	7.495	42.3	28.9	0.1	-2.4
27	7.400	36.9	7.444	43.5	34.3	7.489	54.6	29.3	-8.1	-4.5
28	7.414	41.0	7.451	39.3	37.7	7.467	35.6	34.3	2	0.6
Mean	**7.418**	**38.7**	**7.444**	**44.2**	**35.7**	**7.470**	**44.0**	**31.1**	**1.3**	**-1.4**

ΔPO_2: End-tidal minus arterial PO_2 difference at A12 minus difference at A1
ΔPCO_2: Arterial minus end-tidal PCO_2 difference at A12 minus difference at A1

Table 7B. Arterial blood gas values of 21 menstrual cycle women during the 2nd and 12th hr at altitude.

	C12		A1			A12			A12-A1	
Subj. #	pHa	$PaCO_2$	pHa	PaO_2	$PaCO_2$	pHa	PaO_2	$PaCO_2$	ΔPO_2	ΔPCO_2
2F			7.440	50.0	36.0	7.465	50.5	31.5	1.7	-3.1
2L	7.357	36.7	7.440	43.0	29.0	7.465	47.5	26.0	-3.7	-2.2
4F			7.430	44.0	35.5	7.470	48.5	30.0	-8.4	-6.3
4L	7.40	33.5	7.430	45.0	30.0	7.450	49.0	25.0	-1.9	0.2
6F	7.425	34.0	7.465	52.0	31.0	7.495	63.5	25.0	-4.1	-1.4
6L	7.448	33.9	7.475	49.9	29.4	7.467	40.8	29.5	3.7	1.2
8F	7.435	38.3	7.436	39.3	37.5	7.466	37.2	32.0		
8L	7.435	37.5	7.445	42.5	35.0	7.450	39.0	32.0	5.8	1.5
13F	7.461	35.0	7.470	40.8	33.6	7.563	45.4	28.0	2.1	-0.7
13L	7.472	29.0	7.481	44.1	29.4	7.525	47.1	24.1	-1.1	-1.8
16F	7.403	40.6	7.417	43.6	37.3	7.449	40.1	32.2	4.1	-1.7
16L	7.411	38.3	7.435	41.0	34.7	7.454	40.5	32.2	2.0	-0.1
18F	7.398	37.2	7.435	44.8	32.1	7.445	46.3	31.9	2.1	-0.7
18L	7.413	37.0	7.444	45.9	29.9					
21F	7.420	38.8	7.436	40.3	34.7	7.437	39.4	32.3	-1.5	0.1
21L	7.412	36.1	7.441	48.5	34.9	7.434	45.0	31.8	1.2	1.9
29F	7.477	31.9	7.474	44.3	32.0	7.476	40.3	30.1	-0.8	-1.9
29L	7.432	34.8	7.458	43.0	31.2	7.473	40.1	28.2	1.2	1.2
30F										
30L	7.437	37.7	7.454	43.8	33.3	7.466	38.7	29.8	4.9	0.9
31F	7.418	33.3	7.429	42.7	31.3	7.462	42.4	27.4	2.1	-0.6
31L	7.424	28.1	7.431	50.4	29.5	7.466	50.0	25.4	1.0	-0.1
37F			7.477	48.5	30.8	7.562	57.4	20.2	4.4	-0.1
37L	7.424	34.7	7.474	39.6	30.1	7.461	41.8	29.0	-2.5	0.8
38F	7.406	38.7	7.410	36.0	38.0	7.446	38.8	29.6	-6.7	-9.6
38L	7.397	39.3	7.472	45.5	30.1	7.522	43.7	24.7	8.1	3.5
39F	7.390	38.0	7.400	56.0	30.0	7.478	42	27.7	18.8	5.3
39L	7.397	33.5	7.474	41.6	28.5	7.487	44.1	25.7	-1.7	-1.2
41F	7.393	37.3	7.440	46.4	32.7	7.450	38.6	29.7		
41L	7.412	35.4	7.426	41.1	33.2	7.475	40.4	26.2	1.2	0.4
43F	7.419	35.9	7.468	44.3	32.3	7.476	43.6	28.1	2.9	-0.1
43L	7.421	33.2	7.464	41.9	28.6	7.452	42.0	27.4	3.1	1.1
44F			7.487	39.3	34.1	7.486	39.3	28.9	2.3	-0.4
44L			7.472	39.4	32.0	7.483	40.1	25.8	1.9	-1
45F										
45L	7.422	36.9	7.469	42.5	33.2	7.490	39.0	26.8	1.2	0.3
46F	7.388	38.4	7.478	48.7	30.5	7.485	44.8	27.9	5.0	0.6
46L	7.423	36.5	7.474	41.4	32.4	7.450	37.0	30.0	9.6	3.8
11F	7.420	38.2	7.462	48.8	34.0	7.466	46.2	32.6	4.7	1.1
11L										
23F	7.394	36.5	7.434	45.5	32.1	7.448	45.6	29.1	-0.9	-0.1
23L										
Mean F	**7.416**	**36.8**	**7.447**	**45.0**	**33.4**	**7.475**	**44.7**	**29.2**	**1.6**	**-1.2**
Mean L	**7.419**	**35.1**	**7.456**	**43.7**	**31.3**	**7.471**	**42.5**	**27.8**	**1.9**	**0.6**

ΔPO_2: End-tidal minus arterial PO_2 difference at A12 minus difference at A1

ΔPCO_2: Arterial minus end-tidal PCO_2 difference at A12 minus difference at A1

Table 7C. Arterial blood gas values of 21 women on oral contraceptives during the 2nd and 12th hr (A1, A12) at altitude.

	C12		A1			A12			C12	
Subj. #	pHa	$PaCO_2$	pHa	PaO_2	$PaCO_2$	pHa	PaO_2	$PaCO_2$	ΔPO_2	ΔPCO_2
4C	7.429	34.4	7.467	46.0	30.0	7.479	46.4	26.3	2.2	1.8
4P										
6C										
6P	7.421	33.2	7.445	45.5	30.9	7.450	41.1	28.9	3.4	0.7
16C	7.412	36.6	7.441	42.9	35.0	7.450	41.8	30.7	1.1	-0.1
16P	7.416	36.6	7.415	43.5	35.2	7.450	42.5	29.1	2.3	-3.3
21C										
21P	7.408	36.5	7.450	36.7	33.4	7.446	37.4	29.3	1.0	0.6
29C										
29P	7.442	34.3	7.475	41.8	30.0	7.501	39.0	26.4	3.6	-0.2
32C	7.428	36.9	7.437	45.9	34.1	7.460	43.4	31.9	4.6	1.2
32P	7.429	33.9	7.447	44.0	32.4	7.440	41.4	31.5	1.4	-0.6
33C	7.443	33.0	7.474	44.6	29.5	7.515	42.1	24.9	3.4	-1.6
33P										
34C	7.406	35.1	7.445	38.4	35.6	7.453	40.9	31.8		
34P										
35C	7.427	30.8	7.418	48.4	31.1	7.457	44.4	28.0	3.1	-0.6
35P			7.459	48.4	28.4	7.441	42.9	27.9	4.5	0.5
36C			7.437	43.3	32.5	7.459	45.1	29.6	-0.1	1.7
36P	7.422	34.3	7.443	44.7	30.5	7.464	39.9	28.4	2.6	0.9
37C										
37P	7.423	36.3	7.462	41.5	30.8	7.507	44.9	25.4	4.0	0.7
38C										
38P	7.435	37.5	7.462	37.1	32.3	7.459	41.9	26.5	1.5	-1.0
40C										
40P										
42C			7.469	32.9	37.1					
42P	7.415	37.1	7.456	35.2	33.8	7.477	38.7	31.2	1.8	0.7
44C										
44P	7.440	36.6	7.483	34.7	31.1	7.501	38.3	27.0	0.4	0.9
45C	7.407	35.7	7.457	38.7	31.6	7.476	38.3	25.7	4.4	1.5
45P	7.437	34.8	7.465	37.0	31.5	7.513	36.7	24.3	5.4	0.7
47C			7.461	38.8	32.2	7.490	38.3	29.0	-0.7	-0.2
47P			7.450	38.2	35.1	7.466	35.8	32.2	0.5	-0.9
48C	7.430	36.3	7.464	45.1	32.4	7.475	39.5	28.6	3.6	-1.9
48P			7.449	39.2	30.4	7.460	41.5	25.9	2.5	-0.9
49C	7.419	35.3	7.457	40.6	32.2	7.472	38.4	29.1	2.9	1.3
49P	7.419	36.5	7.475	41.4	29.8	7.457	43.0	29.4		
50C	7.424	39.0	7.451	42.8	35.9	7.450	40.6	33.6		
50P	7.431	35.7	7.488	39.4	30.5	7.482	40.9	30.9	2.8	-0.6
26C										
26P	7.453	29.4	7.523	50.3	24.5	7.540	52.4	21.0	4.8	0.3
Mean C	**7.423**	**35.3**	**7.452**	**42.2**	**33.0**	**7.470**	**41.6**	**29.1**	**2.5**	**0.3**
Mean P	**7.428**	**35.2**	**7.462**	**41.1**	**31.2**	**7.474**	**41.1**	**28.0**	**2.7**	**-0.1**

ΔPO_2: End-tidal minus arterial PO_2 difference at A12 minus difference at A1.

ΔPCO_2: Arterial minus end-tidal PCO_2 difference at A12 minus difference at A1.

Table 8A. HR, MBP and body temperature before and during altitude in 18 men.

	HR (bpm)				MBP (mm Hg)				Temp (degrees F)			
Subj. #	C12	A1	A6	A12	C12	A1	A6	A12	C12	A1	A6	A12
0	73	80	92	86	87	86	82	92	97.4			
1	58	74	80	76	94	77	82	94			97.3	
3	56	57	71	71	84	74	75	80	97.5	96.7	97.5	98.1
5	66	75	81	79	102	84	95	92	98.0	97.7	97.8	98.3
7	46	69	72	73	95	85	72	103	96.9	97.1	98.1	97.9
9	42	62	74	74	89	82	82	85	97.2	96.8	96.7	98.2
10	66	78	86	91	94	100	98	91	96.9	97.3	97.6	98.1
12	60	69	76	77	95	91	89	98	97.6	98.0	97.6	97.7
14	45	81	76	75	88	96	91	98	97.9	97.8	98.5	99.3
15	60	72	77	68	79	70	74	82	98.6	98.9	98.7	99.1
17	54	68	79	74	85	85	83	83	94.9	96.9	96.8	98.2
19	69	69	71	72	84	70	70	83	98.1	98.0	97.6	98.1
20	57	77	78	74	86	72		79	97.7	98.1		99.4
22	59	63	79	73	77		138	95	97.9		97.8	97.8
24	47	71	74	74	93	83	94	98	96.8	97.2	97.4	97.7
25	54	86	88	84	93	89	89	93	97.1	98.2	96.4	98.8
27	48	58	61	60	77	84	73	72	97.7	98.0	98.0	98.8
28	45	76	80	81	77	76	93	80	97.6	98.1	98.4	98.5
Mean	**56**	**71**	**78**	**76**	**88**	**83**	**87**	**89**	**97.4**	**97.7**	**97.6**	**98.4**
P vs. C12		**<0.001**	**<0.001**	**<0.001**		0.11	0.87	0.52		0.11	0.14	**<0.001**

Table 8B. HR, MBP and body temperature before and during altitude in 21 menstrual cycle women.

	HR (bpm)				MBP (mm Hg)				Temp (degrees F)			
Subj. #	C12	A1	A6	A12	C12	A1	A6	A12	C12	A1	A6	A12
2F	69	75	86	86	77	80	81	95	98.0	97.1	97.7	98.2
2L	69		70		96	84	91					
4F	67	73	80	88	79	90	88	74	97.1	98.1		98.7
4L	62	65	78	82	81	80	73	83	97.8	98.2	96.9	98.3
6F	64	73	97	76	88	81	74	95	98.0	98.2	97.9	98.1
6L	71	78	99	82	89	66		78	98.0	97.5		99.1
8F	52	62	73	**73**	84	78	77	**77**	97.7	97.6	97.2	**97.2**
8L	66	71	77	**77**	88	72	79	**79**	98.5	97.7	98.0	**98.0**
13F	56	75	78	75	74	71	72	74	97.3		98.2	98.7
13L	54	60	85	72	73	74	80	80	98.9	97.9	96.9	99.0
16F	58	73	75	96	82	84	80	83	97.9	97.2	97.5	98.7
16L	59	76	81	76	78	79	79	80	97.6	97.7		98.4
18F	67	75	98	90	79	82	97	96	97.8	97.7	97.4	98.2
18L	78	101	107	97	80	92	83	96	98.8	97.9	98.5	98.4
21F	61	68	75	82	99	75	82	90	96.8	97.9	97.4	98.2
21L	77	84	83	77	80	75	82	95	98.9	98.3	97.9	98.4
29F	68	82	95	90	85	80	85	91	97.6	98.0	98.3	98.4
29L	66	81	105	83	75	82	84	84	98.4	97.9	98.4	97.4
30F	76	99	99	100	89	96	91		98.0	98.0	98.5	99.2
30L	70	98	97	98	76	81	100	94	98.7	98.8	98.2	99.2
31F	62	81	84	75	74	78	77	92	97.6	96.8	98.4	98.1
31L	60	79	82	83	81	73	83	87	98.1	98.4	98.7	98.4
37F	56	73	71	70	88	85	93	92	98.1	97.8	98.1	98.9
37L	69	81	81	78	98	92	90	85	99.0	98.4	97.0	99.3
38F	61	67	76	81	85	70	70	76	98.1	96.1	95.6	97.0
38L	63	78	90	75	79	80	71	73	97.0		98.7	98.0
39F	54	79	83	**83**	81	78	87	**87**	97.9		97.9	**97.9**
39L	62	75	85	**85**	78	83	80	**80**	97.1	97.1	98.6	**98.6**
41F	68	78	85	80	93	98	82	89	96.6	97.1	96.2	97.1
41L	70	90	93	96	84		80	85	98.0		97.4	98.1
43F	68	81	88	89	79	72	74	76	97.6	98.3	98.4	98.4
43L	68	84	77	82	75	77	80	75	99.0	98.4	96.5	97.9
44F	74	94	100	94	77	74	97	101	98.3	97.8	98.1	98.0
44L	93	95	98	100	83	93	93	94	99.3	99.2	99.1	98.6
45F	75	92	92	91	79	108	91	82	98.0	98.3	97.1	95.5
45L	78	93	83	103	81	76	74	86	98.7	98.7	98.2	99.1
46F	55	62	71	71	77	74	86	77	97.7	97.8	97.1	98.3
46L	63	67	80	80	77	76	84	84	98.3	98.6	98.7	98.0
11F	50	67	61	66	82	69	68	81	96.5	96.7	96.7	97.8
11L												
23F	65	84	94	100	80	72	85	82	97.8	98.7	98.2	98.2
23L												
Mean F	**63**	**77**	**84**	**84**	**82**	**81**	**83**	**85**	**97.6**	**97.6**	**97.6**	**98.0**
F vs. C12		**<0.001**	**<0.001**	**<0.001**		0.46	0.88	0.13		1.00	0.69	0.07
Mean L	**68**	**81**	**87**	**85**	**82**	**80**	**83**	**84**	**98.3**	**98.2**	**98.0**	**98.5**
L vs. C12		**<0.001**	**<0.001**	**<0.001**		0.40	0.53	0.12		**0.031**	0.16	0.50
F vs. L	**0.014**	0.10	0.22	0.57	0.64	0.68	0.45	0.33	**0.003**	**0.002**	0.18	0.09

Table 8C. HR, MBP and body temperature before and during altitude in 21 women taking oral contraceptives.

	HR (bpm)				MBP (mm Hg)				Temp (degrees F)			
Subj. #	C12	A1	A6	A12	C12	A1	A6	A12	C12	A1	A6	A12
4C	61	78	90	86	91	71	79	75		97.3		98.1
4P	65	81	87	94	86	69	73	89	98.3	98.6	98.6	97.7
6C	67	77	87	85		76	75	92		96.9	97.6	98.7
6P	65	76	85	80	82							
16C	58	73	88	85	89	78	95	84	97.8	98.4	98.1	98.1
16P	61	75	83	84	74	76	72	83	98.4	98.6	98.6	98.5
21C	55	80	81	88	83	89	81	83		98.4	96.5	97.6
21P	84	83	95	101	108	72	80	85	97.3	97.0	97.8	98.4
29C	65	82	89	84	98	85	89	87	96.4			
29P	61	82	92	81	86	72	94	88	97.2	98.0	97.8	98.9
32C	64	87	90	89	83	83	95	84	98.1	97.1	98.2	98.5
32P	69	85	88	86	84	78	78	81	98.1	98.2	98.7	99.1
33C	54	65	69	59	83	71	76	77	97.5	97.6	98.5	98.7
33P	51	64	71	71	67	83	76	85	98.9	98.1	97.7	99.1
34C	66	80	90	87	102	99	104	108		97.5	97.6	98.0
34P	64	91	103	100	91	78	103	98	97.8	97.6	98.1	97.4
35C	71	84	89	92	99	74	89	100	97.3	97.8	98.5	98.5
35P	72	90	100	92	76	89	89	81	98.1	98.3	97.1	99.2
36C	78	92	99	82	81	78	85	89	98.3	98.0	98.6	96.8
36P	73	89	92	88	80	74	83	90	98.6	98.5		98.3
37C	66	83	79	81	97	91	89	99				
37P	66	78	80	75	94	84	89	90		98.6	97.9	98.5
38C	63	82	84	89	86	84	83	92	97.8	97.4	98.0	99.4
38P	71	89	89	106	72	72	76	79	97.0	96.8	97.3	99.0
40C	66	91	87	83	83	86	82	84	97.7	97.9	98.0	97.8
40P	69	86	86	77	85	84	89	84	97.9	97.2	97.3	98.2
42C	76	85	106	110	79	77	90	101	98.8	97.6	97.7	97.2
42P	73	78	97	111	79	79	79	88	97.7	97.5	98.7	97.9
44C	83	92	108	102	89	103	78	100				
44P	73	87	99	93	84	80	94	96	98.0	97.8	97.2	97.9
45C	81	86	89	98	81	81	88	86	97.3	98.4	96.3	98.5
45P	79	88	106	90	81	78	84	84	98.0	98.7		98.3
47C	79	87	89	100	81	85	77	81	98.2			98.8
47P	102	79	99	92	75	82	67	86	96.7	98.6	97.8	97.8
48C	69	95	90	102	85	80	90	92	98.1			
48P	65	90	136	105	83	86	98	99		97.4	98.3	
49C	60	76	70	91	114	100	93	111		97.6	98.8	98.3
49P	64		78	89	105							
50C	54	69	71	89	89	101	95	100	97.5	97.9	98.2	98.4
50P	63	71	93	83	82	102	88	97			99.1	
26P	54	57	64	64	106	100	93	115	97.7	98.1	97.2	97.9
Mean C	**67**	**82**	**87**	**89**	**89**	**85**	**87**	**91**	**97.8**	**97.7**	**97.9**	**98.2**
C vs. C12		**<0.001**	**<0.001**	**<0.001**		0.09	0.39	0.20		1.00	0.42	0.24
Mean P	**69**	**81**	**92**	**89**	**85**	**81**	**84**	**89**	**97.9**	**98.0**	**98.0**	**98.4**
P vs. C12		**<0.001**	**<0.001**	**<0.001**		0.32	0.83	**0.022**		0.47	0.78	**0.019**
C vs. P	0.21	0.79	0.06	0.66	**0.037**	0.10	0.19	0.23	0.65	0.53	0.72	0.27

Table 9A. Extracellular water, total body water and intracellular water on control day and during altitude in 18 men.

		Extracellular water (L)			Total body water (Kg)			Intracellular water (L)		
Subj. #	**Wt (Kg)**	**C12**	**A12**	**Δ%**	**C12**	**A12**	**Δ%**	**C12**	**A12**	**Δ%**
0	72.3	15.28	16.48	7.9	48.6	46.3	-4.7	33.3	29.8	-10.5
1	69.8	15.82	16.58	4.8	46.0	44.0	-4.3	30.2	27.4	-9.1
3	78.1	18.55	18.34	-1.1	50.5	46.9	-7.1	32.0	28.6	-10.6
5	98.5	18.55	29.13	57.0	50.6	57.1	12.8	32.1	28.0	-12.7
7	67.9	15.47	13.79	-10.9	44.2	44.7	1.1	28.7	30.9	7.6
9	89.6	18.88	25.28	33.9	56.8	62.9	10.7	37.9	37.6	-0.8
10	93.2	16.13	N		50.5	N		34.4	N	
12	95.2	18.77	20.50	9.2	54.5	55.0	0.9	35.7	34.5	-3.4
14	80.7	18.74	18.48	-1.4	55.1	52.8	-4.2	36.4	34.3	-5.6
15	64.4	14.91	15.58	4.5	42.2	42.0	-0.5	27.3	26.4	-3.2
17	80.1	16.49	15.80	-4.2	49.6	45.7	-7.9	33.1	29.9	-9.7
19	77.3	16.28	15.46	-5.0	49.7	48.6	-2.2	33.4	33.1	-0.8
20	59.8	13.82	13.40	-3.0	38.6	38.4	-0.5	24.8	25.0	0.9
22	91.4	18.12	29.71	64.0	52.6	55.7	5.9	34.5	26.0	-24.6
24	56.2	12.94	13.52	4.5	38.0	42.7	12.4	25.1	29.2	16.4
25	77.1	17.74	18.23	2.8	46.9	43.1	-8.1	29.2	24.9	-14.7
27	65.2	13.56	12.58	-7.2	42.9	42.1	-1.9	29.3	29.5	0.6
28	82.1	19.61	25.79	31.5	57.7	63.6	10.2	38.1	37.8	-0.7
Mean	**77.7**	**16.65**	**18.74**	**11.0**	**48.6**	**48.9**	**0.7**	**32.0**	**30.2**	**-4.8**

N: Not available because of vomiting

Table 9B. Extracellular water, total body water and intracellular water on control day and during altitude in 21 menstrual cycle women.

		Extracellular water (L)			Total body water (Kg)			Intracellular water (L)		
Subj. #	Wt (Kg)	C12	A12	Δ%	C12	A12	Δ%	C12	A12	Δ%
2F	71.9	14.63	14.48	-1.0	37.5	35.8	-4.5	22.9	21.3	-6.8
2L		14.03	13.32	-5.1	36.6	38.4	4.9	22.6	25.1	11.1
4F	50.0	9.33	10.05	7.7	25.0	24.2	-3.2	15.7	14.2	-9.7
4L		9.22	8.79	-4.7	24.9	23.7	-4.8	15.7	14.9	-4.9
6F	52.3	9.70	11.69	20.5	27.5	28.2	2.5	17.8	16.5	-7.2
6L		10.67	10.35	-3.0	28.2	29.0	2.8	17.5	18.7	6.4
8F	85.5	14.94	N		39.9	N		25.0	N	
8L		16.32	N		44.4	N		28.1	N	
13F	54.6	11.64	12.16	4.5	31.6	32.6	3.2	20.0	20.4	2.4
13L		11.21	10.66	-4.9	29.8	30.0	0.7	18.6	19.3	4.0
16F	55.8	10.14	9.94	-2.0	26.3	27.4	4.2	16.2	17.5	8.0
16L		10.17	9.77	-3.9	26.8	28.2	5.2	16.6	18.4	10.8
18F	60.6	12.54	13.40	6.9	33.2	33.3	0.3	20.7	19.9	-3.7
18L		**13.40**	**12.14**	**-9.4**	**32.8**	**40.6**	**23.8**	**19.4**	**28.5**	**46.7**
21F	64.2	15.79	N		41.3	N		25.5	N	
21L		13.76	N		38.6	N		24.8	N	
29F	82.2	14.76	14.43	-2.2	41.5	37.0	-10.8	26.7	22.6	-15.6
29L		14.05	10.96	-22.0	36.4	36.9	1.4	22.4	25.9	16.1
30F	88.0	**17.73**	**19.69**	**11.1**	**41.4**	**50.6**	**22.2**	**23.7**	**30.9**	**30.6**
30L		16.37	15.83	-3.3	42.1	44.2	5.0	25.7	28.4	10.3
31F	58.2	12.56	13.01	3.6	33.0	28.0	-15.2	20.4	15.0	-26.7
31L		11.01	21.84	98.4	30.2	35.8	18.5	19.2	14.0	-27.3
37F	62.8	13.34	13.22	-0.9	35.9	35.6	-0.8	22.6	22.4	-0.8
37L		11.88	12.89	8.5	33.9	34.8	2.7	22.0	21.9	-0.5
38F	56.2	11.56	N		30.0	N		18.4	N	
38L		**11.92**	**27.66**	**132.0**	**31.1**	**43.7**	**40.5**	**19.2**	**16.0**	**-16.4**
39F	73.7	15.19	N		33.3	N		18.1	N	
39L		12.88	N		31.3	N		18.4	N	
41F	73.2	13.13	15.30	16.5	34.6	33.0	-4.6	21.5	17.7	-17.6
41L		16.37	N		37.0	N		20.6	N	
43F	60.1	13.78	16.31	18.4	34.7	37.3	7.5	20.9	21.0	0.3
43L		13.02	13.40	2.9	35.2	35.2	0.0	22.2	21.8	-1.7
44F	91.2	14.53	15.11	4.0	36.5	42.6	16.7	22.0	27.5	25.1
44L		15.16	14.73	-2.8	36.9	35.7	-3.3	21.7	21.0	-3.5
45F	63.5	10.80	18.42	70.6	34.8	38.2	9.8	24.0	19.8	-17.6
45L		13.59	18.67	37.4	34.9	36.3	4.0	21.3	17.6	-17.3
46F	54.0	9.31	10.48	12.6	31.1	30.9	-0.6	21.8	20.4	-6.3
46L		10.42	8.24	-20.9	29.6	30.5	3.0	19.2	22.3	16.1
11F	59.2	12.69	12.41	-2.2	33.7	33.4	-0.9	21.0	21.0	-0.1
11L										
23F	52.4	12.60	13.33	5.8	29.3	33.3	13.7	16.7	20.0	19.6
23L										
Mean F	**65.2**	**12.65**	**13.36**	**10.2**	**33.5**	**33.2**	**1.1**	**20.9**	**19.8**	**-3.5**
Mean L	**65.2**	**12.95**	**13.03**	**5.9**	**33.9**	**33.7**	**3.1**	**21.0**	**20.7**	**1.5**

N: Not available because of vomiting

Bold and large: not included in statistics

Table 9C. Extracellular water, total body water and intracellular water on control day and during altitude in women taking oral contraceptives.

		Extracellular water (L)			Total Body water (Kg)			Intracellular water (L)		
Subj. #	Wt (kg)	C12	A12	Δ%	C12	A12	Δ%	C12	A12	Δ%
4C	50.0	9.23	8.83	-4.3	24.7	24.3	-1.6	15.5	15.5	0.0
4P		8.55	N		23.0	N		14.5	N	
6C	55.1	11.35	10.66	-6.1	26.1	26.3	0.8	14.8	15.6	6.0
6P		12.05	10.86	-9.9	31.7	28.4	-10.4	19.7	17.5	-10.7
16C	54.3	9.35	N		28.5	N		19.2	N	
16P		10.16	9.26	-8.9	28.0	25.2	-10.0	17.8	15.9	-10.7
21C	61.5	16.69	N		36.3	N		19.6	N	
21P		**15.27**	**53.77**	**252.1**	**36.8**	**46.0**	**25.0**	**21.5**	**-7.8**	**-136.1**
29C	79.5	11.43	16.56	44.9	36.6	39.6	8.2	25.2	23.0	-8.5
29P		13.58	13.33	-1.8	37.1	35.6	-4.0	23.5	22.3	-5.3
32C	86.6	16.68	17.19	3.1	36.8	39.2	6.5	20.1	22.0	9.4
32P		15.43	17.37	12.6	37.6	39.8	5.9	22.2	22.4	1.2
33C	74.1	14.64	16.63	13.6	36.4	37.7	3.6	21.8	21.1	-3.2
33P		13.97	12.65	-9.4	40.1	40.6	1.2	26.1	28.0	7.0
34C	63.7	11.95	N		33.9	N		22.0	N	
34P		11.08	9.05	-18.3	30.7	30.8	0.3	19.6	21.8	10.9
35C	52.5	11.14	10.66	-4.3	24.9	25.6	2.8	13.8	14.9	8.6
35P		9.01	10.08	11.9	27.1	25.7	-5.2	18.1	15.6	-13.7
36C	57.5	10.41	12.56	20.7	29.3	34.5	17.7	18.9	21.9	16.1
36P		10.16	11.10	9.3	29.0	28.3	-2.4	18.8	17.2	-8.7
37C	62.9	15.12	12.27	-18.8	38.9	35.2	-9.5	23.8	22.9	-3.6
37P		14.34	17.34	20.9	36.8	35.2	-4.3	22.5	17.9	-20.5
38C	58.2	9.35	9.24	-1.2	30.4	29.8	-2.0	21.1	20.6	-2.3
38P		12.41	10.40	-16.2	31.4	30.2	-3.8	19.0	19.8	4.3
40C	56.7	12.25	12.36	0.9	28.2	28.3	0.4	16.0	15.9	-0.1
40P		11.47	11.79	2.8	29.0	26.2	-9.7	17.5	14.4	-17.8
42C	61.5	12.46	12.40	-0.5	33.5	36.7	9.6	21.0	24.3	15.5
42P		12.34	12.40	0.5	33.1	33.4	0.9	20.8	21.0	1.2
44C	90.6	14.16	N		35.5	N		21.3	N	
44P		13.48	N		35.7	N		22.2	N	
45C	65.2	14.26	N		33.8	N		19.5	N	
45P		13.18	N		32.6	N		19.4	N	
47C	63.1	12.51	15.07	20.5	29.7	32.6	9.8	17.2	17.5	2.0
47P		**12.74**	**41.26**	**223.9**	**30.7**	**46.1**	**50.2**	**18.0**	**4.8**	**-73.1**
48C	66.7	10.90	N		32.3	N		21.4	N	
48P		13.76	N		33.4	N		19.6	N	
49C	59.9	14.05	15.00	6.8	34.5	34.8	0.9	20.5	19.8	-3.2
49P		15.93	15.82	-0.7	36.3	34.4	-5.2	20.4	18.6	-8.8
50C	62.3	16.66	18.77	12.7	37.4	37.5	0.3	20.7	18.7	-9.7
50P		14.88	12.82	-13.8	33.1	32.7	-1.2	18.2	19.9	9.1
26C	67.3									
26P		13.11	13.15	0.3	36.2	36.0	-0.6	23.1	22.9	-1.0
Mean C	**64.2**	**12.73**	**13.44**	**6.3**	**32.4**	**33.0**	**3.4**	**19.7**	**19.6**	**1.9**
Mean P	**64.2**	**12.57**	**12.49**	**-1.4**	**32.7**	**32.2**	**-3.2**	**20.2**	**19.7**	**-4.2**

N: Not available because of vomiting

Bold and large: not included in statistics

Table 10A. Plasma volume (ml), change in PV with altitude (Δ%PV) by 4 methods and TCER (%/hr) on control day (C12) and at altitude in 18 men.

							TCER		
Subj. #	**C12**	**A12**	**$\Delta\%PV_E$**	**$\Delta\%PV_{TP}$**	**$\Delta\%PV_{HH}$**	**$\Delta\%PV_{PD}$**	**C12**	**A12**	**Diff.**
0	3416	3887	13.8	-3.5	-1.2	2.2	-3.9	-9.8	-5.9
1	3311	3501	5.7	-8.2	-7.1	-5.6	-0.1	-7.8	-7.7
3	5226	4679	-10.5	-10.5	-6.8	-3.5	-1.8	-1.5	0.3
5	3761	4046	7.6	-2.7	6.6	-4.1	0.7	-2.6	-3.3
7	4266	4181	-2.0	3.0	1.2	1.9	-14.5	-8.0	6.5
9	3819	4296	12.5	-1.4	-1.1		-9.0	-8.3	0.7
10	3528	N		-9.2	-5.2		-5.5	N	
12	4268	4227	-1.0	-1.4	-12.9	-9.0	-7.2	-5.1	2.1
14	5037	4457	-11.5	0.0	2.8	-1.5	-5.8	-8.0	-2.2
15	3959	4346	9.8	6.5	5.9	3.4	-2.5	-14.8	-12.3
17	3588	3732	4.0	4.2	-7.4	-7.7	-6.7	-6.8	-0.1
19	4498	3949	-12.2	-4.3	-6.0	-5.2	-3.0	-5.8	-2.8
20	4104	3673	-10.5	4.4	4.2	4.6	-14.2	-5.6	8.6
22	4871	4311	-11.5	-6.9	-5.5	-4.1	-10.5	-9.0	1.5
24	3252	3357	3.2	-17.2	-12.8	-5.1	-4.2	6.8	11.0
25	4783	3082	-35.6	-6.7	-10.0	-5.8	-24.7	-11.6	13.1
27	3405	3216	-5.6	-1.5	-0.8	1.8	-7.8	-8.2	-0.4
28	4242	3923	-7.5	-7.1	-11.2	-8.6	-21.4	-9.0	12.4
Mean	**4074**	**3933**	**-3.0**	**-3.5**	**-3.7**	**-2.9**	**-7.9**	**-6.8**	**1.3**

N: Not measured

Table 10B. Plasma volume (ml), change in PV with altitude (Δ%PV) by 4 methods and TCER (%/hr) on control day (C12) and at altitude in 21 menstrual cycle women.

							TCER		
Subj. #	**C12**	**A12**	**$\Delta\%PV_E$**	**$\Delta\%PV_{TP}$**	**$\Delta\%PV_{HH}$**	**$\Delta\%PV_{PD}$**	**C12**	**A12**	**Diff.**
2F	3327	3492	5.0	-12.2	-24.0	-9.9	-7.5	-3.8	3.7
2L	3518	2894	-17.7	-8.2	-7.6	-11.2	-5.6	-12.8	-7.2
4F	2080	1993	-4.2	6.2	5.6	-8.7	-10.2	-8.4	1.8
4L	2210	1995	-9.7	-2.9	-12.0	-4.0	-4.4	-6.4	-2.0
6F	2527	2488	-1.5	1.4	-3.5	5.5	-4.9	-1.5	3.4
6L	2674	2121	-20.7	-3.9	-2.5	-18.4	-0.7	-10.2	-9.5
8F	4405	3306	-24.9	-1.4	-10.1	-0.6	-7.4	-11.9	-4.5
8L	4294	4510	5.0	-4.1	-4.9	1.5	-4.7	N	
13F	2762	2366	-14.3	-4.8	-9.1	-2.7	-9.4	-9.1	0.3
13L	2975	2740	-7.9	3.3	5.7	-2.4	-7.0	-4.5	2.5
16F	2718	2354	-13.4	-4.1	3.9	-3.6	-6.4	-2.2	4.2
16L	3426	2793	-18.5	-9.5	-7.5	-6.8	5.1	-15.5	-20.6
18F	3845	2865	-25.5	-9.6	-20.3	-24.0	-7.5	-8.4	-0.9
18L	3582	3049	-14.9	-5.6	0.7	-5.9	-4.6	-5.4	-0.8
21F	4052	3912	-3.5	1.4	0.3	0.8	-3.6	1.7	5.3
21L	3291	3813	15.9	8.5	16.4	10.5	-6.8	-2.8	4.0
29F	3718	3545	-4.7	1.4	-11.8	-3.4	-4.0	-2.2	1.8
29L	3768	3728	-1.1	0.0	-12.9	-2.5	-4.4	-2.3	2.1
30F	4717	4262	-9.6	0.0	5.5	7.2	0.1	-5.4	-5.5
30L	4235	4219	-0.4	-5.7	-17.3	-10.2	-5.4	-0.7	4.7
31F	3037	3103	2.2	-17.9	-7.8	-21.0	-9.9	-1.1	8.8
31L	2676	3005	12.3	-6.7	11.0		-8.4	-2.8	5.6
37F	3377	3242	-4.0	-2.8	-3.7	1.1	-6.8	-7.0	-0.2
37L	3571	3249	-9.0	-5.3	-8.4		-4.9	-6.0	-1.1
38F	2995	2920	-2.5	-9.9	-12.9	-13.3	-3.4	16.9	20.3
38L	3321	2853	-14.1	-4.4	12.8	-0.1	7.4	2.0	-5.4
39F	2839	2629	-7.4	-13.2	-13.0	16.3	-6.5	N	
39L	3792	2849	-24.9	-4.4	-7.2	-5.4	-1.2	-14.6	-13.4
41F	3481	2872	-17.5	-17.7	-20.1	-13.6	-5.3	-9.6	-4.3
41L	3052	3170	3.9	-7.4	-4.5	-8.4	-9.0	N	
43F	3653	3244	-11.2	-4.5	4.2	-8.7	-7.5	-6.5	1.0
43L	3177	3042	-4.2	-9.9	-1.6	-6.2	-5.3	-9.3	-4.0
44F	3479	3167	-9.0	-7.8	-3.3	-6.3	-4.6	-6.9	-2.3
44L	3632	3006	-17.2	-7.0	-8.4	-15.6	-4.3	-8.4	-4.1
45F	3265	3225	-1.2	-5.6	-5.1	-0.7	-4.4	-6.5	-2.1
45L	3537	3069	-13.2	-7.1	4.3	0.6	-2.0	-2.4	-0.4
46F	3685	2684	-27.2	-10.0	-9.1	-11.0	-13.8	-3.4	10.4
46L	3167	2718	-14.2	-5.9	0.0	-7.8	-15.5	-10.9	4.6
11F	3219	2895	-10.1	-4.1	-1.0	-4.5	-0.5	0.8	1.3
11L									
23F	2600	2805	7.9	1.5	3.4	-3.5	-7.2	0.9	8.1
23L									
Mean F	**3323**	**3018**	**-8.4**	**-5.4**	**-6.3**	**-5.0**	**-6.2**	**-3.7**	**2.5**
Mean L	**3363**	**3096**	**-7.9**	**-4.5**	**-2.3**	**-5.4**	**-4.3**	**-6.6**	**-2.6**

N: Not sufficient samples for valid decay slope

Table 10C. Plasma volume (ml), change in PV with altitude (Δ%PV) by 4 methods and TCER (%/hr) on control day (C12) and at altitude in 21 women on OCPs.

							TCER		
Subj. #	**C12**	**A12**	**$\Delta\%PV_E$**	**$\Delta\%PV_{TP}$**	**$\Delta\%PV_{HH}$**	**$\Delta\%PV_{PD}$**	**C12**	**A12**	**Diff.**
4C	2174	2090	-3.9	0.0	10.6	-3.3	-5.6	-7.8	-2.2
4P	2487	2182	-12.3	-8.7	-3.8	-1.6	-7.1	-5.6	1.5
6C	2311	2537	9.8	4.2	12.3	6.6	-5.7	-3.0	2.7
6P	2889	2721	-5.8	-1.4	-13.0	-17.1	-4.8	-1.4	3.4
16C	2557	2547	-0.4	-4.2	4.0	-10.4	-5.8	-2.1	3.7
16P	2803	2587	-7.7	-7.2	-4.1	-16.9	-8.8	-4.6	4.2
21C	3851	3396	-11.8	5.0	17.4	5.7	-1.4	N	
21P	3979	3548	-10.8	-6.0	6.7	-4.0	-4.0	-8.0	-4.0
29C	3629	4838	33.3	-1.4	-10.0	-6.9	-6.8	-12.9	-6.1
29P	4357	3500	-19.7	-15.2	-6.2	15.2	-9.7	-2.4	7.3
32C	3378	3175	-6.0	1.5	-1.4	1.5	-0.9	-11.1	-10.2
32P	3477	3744	7.7	-4.3	-5.5	-2.3	-4.7	2.3	7.0
33C	3780	3820	1.1	4.8	10.9	-10.4	-4.4	-5.5	-1.1
33P	3612	3276	-9.3	-1.4	-7.1		-5.8	-6.7	-0.9
34C	3104	2848	-8.2	-5.6	-5.7	2.1	-7.8	N	
34P	2597	2548	-1.9	4.3	1.5	0.5	-9.8	-12.7	-2.9
35C	2435	2557	5.0	-1.5	9.1	3.8	-0.3	-3.5	-3.2
35P	2372	2296	-3.2	-1.4	-2.0	-2.8	-3.4	-1.2	2.2
36C	3335	2967	-11.0	1.5	1.5	-1.2	-5.2	-8.3	-3.1
36P	2904	2764	-4.8	-4.3	-10.8	-3.5	-7.3	-6.1	1.2
37C	3788	3677	-2.9	-5.5	-2.6	-1.5	-4.3	-7.8	-3.5
37P	3283	3183	-3.0	-2.8	-9.7	-1.2	-11.2	-8.6	2.6
38C	3123	2508	-19.7	0.0	-4.4	-3.0	4.4	-8.6	-13.0
38P	2704	2944	8.9	4.2	12.1	14.0	-5.2	-6.8	-1.6
40C	3021	2733	-9.5	-6.7	-9.9	-4.7	-6.3	-7.3	-1.0
40P	3155	3973	25.9	1.4	5.3	-20.3	-3.5	9.8	13.3
42C	3208	2570	-19.9	-8.1	-3.1	-2.8	0.0	-8.2	-8.2
42P	2882	2822	-2.1	2.9	14.1	2.6	-5.2	-6.4	-1.2
44C	3884	3176	-18.2	-3.0	2.6	-0.1	-1.5	-6.3	-4.8
44P	3658	3067	-16.2	-10.1	-10.6	-6.0	-2.6	N	
45C	3701	2778	-24.9	-9.1	-15.4	-7.9	-3.0	-5.3	-2.3
45P	3576	3460	-3.2	-2.9	2.9	-14.5	-2.5	N	
47C	2778	2945	6.0	8.1	10.8	8.8	-4.8	-5.7	-0.9
47P	2603	3068	17.9	-8.7	7.2	0.1	-2.8	-2.8	0.0
48C	3065	2746	-10.4	-4.3	-5.6	-5.5	-3.2	-6.2	-3.0
48P	2751	2879	4.7	-14.8	-17.1	-7.0	-2.3	-3.3	-1.0
49C	3347	2587	-22.7	1.4	0.4	4.2	-4.0	-12.0	-8.0
49P	3329	3562	7.0	5.9	0.4	9.3	-4.1	-10.4	-6.3
50C	3760	2950	-21.5	-3.9	-19.1	-28.3	-3.8	-6.5	-2.7
50P	5177	3136	-39.4	-8.6	-6.3	-10.6	-5.7	-5.8	-0.1
26C									
26P	3836	3642	-5.1	-1.4	-0.9		1.0	-6.5	-7.5
Mean C	**3211**	**2972**	**-6.8**	**-1.3**	**0.1**	**-2.7**	**-3.5**	**-7.1**	**-3.7**
Mean P	**3259**	**3091**	**-3.5**	**-3.8**	**-2.2**	**-3.5**	**-5.2**	**-4.6**	**0.9**

N: Not sufficient samples for valid decay slope

Table 11A. Urine volume (ml/hr) of 18 men 12 hr before (C12) and at 3, 6, 9 and 12 hr of altitude exposure.

Subj. #	C12	A3	A6	A9	A12	Δ%
0	207	303	333	380	238	21
1	893	580	105	215	147	-75
3	141	443	552	182	271	-22
5	358	382	65	86	200	-61
7	151	387	491	259	293	3
9	775	230	78	103	355	-54
10	173	303	232	33	33	-86
12	409	341	389	289	239	-30
14	683	474	129	305	51	-69
15	259	227	79	308	266	18
17	426	866	427	179	187	-72
19	523	526	482	282	257	-49
20	235	325	127	79	32	-80
22	244	325	200	301	59	-37
24	422	123	338	141	129	-50
25	359	325	406	222	105	-52
27	363	591	574	373	249	-35
28	220	209	100	54	58	-74
Mean	**380**	**387**	**284**	**211**	**176**	**-45**

Δ%: Percent change of A9 and A12 average from C12 and A3 average

Table 11B. Urine volume (ml/hr) of 21 menstrual cycle women 12 hr before (C12) and at 3, 6, 9 and 12 hr of altitude exposure.

Subj. #	C12	A3	A6	A9	A12	Δ%
2F	564	393	415	336	369	-26
2L	330	431	697	361	558	21
4F	110	200	49	23	47	-77
4L	186	163	62	8	140	-58
6F	341	621	601	293	415	-27
6L	226	532	277	183	174	-53
8F	182	391	141	0		-100
8L	533	278	0	0		-100
13F	221	299	513	158	315	-9
13L	265	423	397	416	477	30
16F	188	133	58	44	191	-27
16L	101	240	208	183	128	-9
18F	103	312	126	194	185	-9
18L	130	349	436	265	416	42
21F	103	235	0	89	0	-74
21L	466	637	245	0	90	-92
29F	434	490	161	422	192	-34
29L	311	317	227	61	213	-56
30F	566	560	589	385	249	-44
30L	365	280	710	523	616	77
31F	516	425	522	286	197	-49
31L	333	420	580	131	38	-78
37F	166	134	190	270	312	94
37L	96	304	212	249	191	10
38F	357	70	56	17	17	-92
38L	246	252	243	91	18	-78
39F	428	107	55	24		-91
39L	149	84	27	21		-82
41F	398	624	791	406	200	-41
41L	272	561	349	0	0	-100
43F	859	356	271	56	172	-81
43L	123	298	308	53	337	-7
44F	189	183	217	67	187	-32
44L	185	463	104	171	151	-50
45F	441	411	342	50	41	-89
45L	201	385	118	50	64	-81
46F	173	263	266	457	153	40
46L	230	242	521	230	116	-27
11F	180	211	167	164	210	-4
11L						
23F	115	288	112	154	209	-10
23L						
Mean F	**316**	**319**	**269**	**185**	**193**	**-37**
Mean L	**250**	**350**	**301**	**158**	**219**	**-36**

Δ%: Percent change of A9 and A12 average from C12 and A3 average

Table 11C. Urine volume (ml/hr) of 21 women taking OCPs 12 hr before (C12) and at 3, 6, 9 and 12 hr of altitude exposure.

Subj. #	C12	A3	A6	A9	A12	Δ%
4C	239	289	29	42	62	-80
4P	163	237	137	27	30	-86
6C	275	259	107	70	215	-47
6P	476	91	85	103	144	-56
16C	318	259	49	49	50	-83
16P	486	577	279	71	325	-63
21C	22	171	0	0	189	-2
21P	91	15	101	0	0	-100
29C	231	394	178	129	142	-57
29P	199	362	249	113	111	-60
32C	106	309	312	217	161	-9
32P	214	242	121	185	181	-20
33C	113	423	850	1209	290	180
33P	290	168	765	637	275	99
34C	142	283	42	16		-92
34P	31	204	185	171		46
35C	100	233	249	227	64	-13
35P	249	322	294	125	195	-44
36C	199	360	179	56	55	-80
36P	118	386	151	328	176	0
37C	176	223	305	49	51	-75
37P	50	508	247	176	121	-47
38C	135	69	38	41	32	-64
38P	209	110	39	11	35	-86
40C	44	183	57	140	76	-5
40P	432	75	97	40	38	-85
42C	200	101	389	154	76	-24
42P	176	67	170	187	49	-3
44C	88	263	121	33	29	-82
44P	264	144	0	35		-83
45C	218	36	39	0	280	10
45P	262	349	407	0	132	-78
47C	178	350	475	0	180	-66
47P	203	190	0	399	0	2
48C	68	405	0	78	45	-74
48P	328	0	111	0	70	-79
49C	308	301	114	33	343	-38
49P	217	359	100	73	198	-53
50C	299	161	224	173	116	-37
50P	164	111	167	160	120	2
26P	141	604	353	325	377	-6
Mean C	**173**	**254**	**188**	**136**	**129**	**-37**
Mean P	**227**	**244**	**193**	**151**	**136**	**-38**

Δ%: Percent change of A9 and A12 average from C12 and A3 average

Table12A. Fluid intake, urine volume and intake minus urine volume (ml/hr) in 18 men.

	Fluid intake (ml/hr)					Urine volume (ml/hr)					In minus out (ml/hr)				
Subj. #	**C12**	**A3**	**A6**	**A9**	**A12**	**C12**	**A3**	**A6**	**A9**	**A12**	**C12**	**A3**	**A6**	**A9**	**A12**
0	541	186	73	637	138	137	152	205	237	171	404	34	-132	400	-33
1	410	207	150	233	67	893	580	105	215	147	-483	-373	45	18	-80
3	109	629	345	0	185	141	443	552	182	271	-32	186	-207	-182	-86
5	432	550	300	242	67	358	382	65	86	200	74	168	235	156	-133
7	167	387	197	409	367	151	387	491	259	293	16	0	-294	150	74
9	457	250	167	150	133	775	230	78	103	355	-318	20	89	47	-222
10	171	645	167	35	35	173	303	232	33	33	-2	342	-65	2	2
12	433	366	421	273	17	409	341	389	289	239	24	25	32	-16	-222
14	567	474	179	179	100	683	474	129	305	51	-116	0	50	-126	49
15	620	191	317	54	167	259	227	79	308	266	361	-36	238	-254	-99
17	426	413	278	367	15	426	866	427	179	187	0	-453	-150	188	-172
19	455	400	496	375	100	523	526	482	282	257	-69	-126	14	93	-157
20	233	617	133	133	133	235	325	127	79	32	-2	292	6	54	101
22	300	579	254	217	0	244	325	200	301	59	56	254	54	-84	-59
24	160	452	133	200	100	422	123	338	141	129	-262	329	-205	59	-29
25	200	312	357	246	167	359	325	406	222	105	-159	-13	-49	24	62
27	243	560	797	333	100	363	591	574	373	249	-121	-31	223	-40	-149
28	150	382	440	157	0	220	209	100	54	58	-70	173	340	103	-58
Mean	**337**	**422**	**289**	**236**	**105**	**376**	**378**	**277**	**203**	**172**	**-39**	**44**	**12**	**33**	**-67**

Table12B. Fluid intake, urine volume and intake minus urine volume (ml/hr) in 21 menstrual women.

	Fluid intake (ml/hr)					Urine volume (ml/hr)					In minus out (ml/hr)				
Subj. #	**C12**	**A3**	**A6**	**A9**	**A12**	**C12**	**A3**	**A6**	**A9**	**A12**	**C12**	**A3**	**A6**	**A9**	**A12**
2F	296	585	650	333	309	564	393	415	336	369	-268	192	235	-3	-60
2L	306	520	450	497	200	330	431	697	361	558	-24	89	-247	136	-358
4F	110	355	0	133	146	110	200	49	23	47	0	155	-49	110	99
4L	186	389	79	33	0	186	163	62	8	140	0	226	17	25	-140
6F	341	900	400	550	100	341	621	601	293	415	0	279	-201	257	-315
6L	333	500	67	83	0	226	532	277	183	174	107	-32	-210	-100	-174
8F	183	917	47	0	**0**	182	391	141	0	**0**	1	526	-94	0	**0**
8L	519	657	100	0	**0**	533	278	0	0	**0**	-14	379	100	0	**0**
13F	183	267	433	227	217	221	299	513	158	315	-38	-32	-80	69	-98
13L	375	491	465	567	143	265	423	397	416	477	110	68	68	151	-334
16F	100	134	200	0	125	188	133	58	44	191	-88	1	142	-44	-66
16L	50	200	167	200	71	101	240	208	183	128	-51	-40	-41	17	-57
18F	83	233	146	233	100	103	312	126	194	185	-20	-79	20	39	-85
18L	130	710	383	300	200	130	349	436	265	416	0	361	-53	35	-216
21F	100	379	200	33	0	103	235	0	89	0	-3	144	200	-56	0
21L	333	400	417	333	350	466	637	245	0	90	-133	-237	172	333	260
29F	427	439	231	232	174	434	490	161	422	192	-7	-51	70	-190	-18
29L	350	229	100	180	114	311	317	227	61	213	39	-88	-127	119	-98
30F	333	776	452	579	154	566	560	589	385	249	-233	216	-137	194	-95
30L	203	679	649	531	333	365	280	710	523	616	-162	399	-61	8	-283
31F	443	590	250	300	0	516	425	522	286	197	-74	165	-272	14	-197
31L	296	662	662	417	133	333	420	580	131	38	-38	242	82	286	95
37F	154	409	220	533	0	166	134	190	270	312	-12	275	30	263	-312
37L	116	165	342	154	267	96	304	212	249	191	20	-139	130	-95	76
38F	214	510	40	**56**	**56**	357	70	56	17	17	-142	440	-16	40	40
38L	226	350	350	174	91	246	252	243	91	18	-20	98	107	83	73
39F	272	319	233	0	**0**	428	107	55	**12**	**12**	-155	212	178	**-12**	**-12**
39L	259	379	300	161	**161**	149	84	27	**11**	**11**	110	295	273	**150**	**150**
41F	273	658	700	511	500	398	624	791	406	200	-125	34	-91	105	300
41L	239	496	367	300	250	272	561	349	0	0	-33	-65	18	300	250
43F	769	303	243	200	114	859	356	271	56	172	-89	-53	-28	144	-58
43L	156	392	333	168	183	123	298	308	53	337	33	94	25	115	-154
44F	121	279	50	33	133	189	183	217	67	187	-68	96	-167	-34	-54
44L	263	347	167	179	152	185	463	104	171	151	78	-116	63	8	1
45F	200	250	333	250	129	441	411	342	50	41	-241	-161	-9	200	88
45L	137	30	247	75	83	201	385	118	50	64	-64	-355	129	25	19
46F	150	447	151	525	91	173	263	266	457	153	-23	184	-115	68	-62
46L	286	313	300	112	62	230	242	521	230	116	56	71	-221	-118	-55
11F	100	429	279	167	0	180	211	167	164	210	-80	218	112	3	-210
11L															
23F	344	412	417	81	267	115	288	112	154	209	229	124	305	-73	58
23L															
Mean F	**247**	**457**	**270**	**237**	**125**	**316**	**319**	**269**	**185**	**175**	**-68**	**137**	**2**	**52**	**-50**
Mean L	**251**	**416**	**313**	**235**	**147**	**250**	**350**	**301**	**157**	**197**	**1**	**66**	**12**	**78**	**-50**

Table12C. Fluid intake, urine volume and intake minus urine volume (ml/hr) in 21 women taking OCPs.

	Fluid intake (ml/hr)					Urine volume (ml/hr)					In minus out (ml/hr)				
Subj. #	**C12**	**A3**	**A6**	**A9**	**A12**	**C12**	**A3**	**A6**	**A9**	**A12**	**C12**	**A3**	**A6**	**A9**	**A12**
4C	80	254	112	33	33	239	289	29	42	62	-159	-35	83	-9	-29
4P	100	347	162	133	0	163	237	137	27	30	-63	110	25	106	-30
6C	360	224	100	248	80	275	259	107	70	215	85	-35	-7	178	-135
6P	357	178	58	117	58	476	91	85	103	144	-119	87	-27	14	-86
16C	368	246	100	100	167	318	259	49	49	50	50	-13	51	51	117
16P	464	425	475	67	33	486	577	279	71	325	-22	-152	196	-4	-292
21C	97	250	135	19	0	22	171	0	0	189	75	79	135	19	-189
21P	117	108	194	90	117	91	15	101	0	0	26	93	93	90	117
29C	221	246	146	291	194	231	394	178	129	142	-10	-148	-33	162	52
29P	200	300	250	167	154	199	362	249	113	111	1	-62	1	54	43
32C	333	141	303	182	62	106	309	312	217	161	227	-168	-9	-35	-99
32P	333	667	333	167	0	214	242	121	185	181	119	425	212	-18	-181
33C	253	855	788	709	533	113	423	850	1209	290	140	432	-62	-500	243
33P	250	500	600	417	333	290	168	765	637	275	-40	332	-165	-220	59
34C	143	259	0	50	50	142	283	42	16	**16**	1	-24	-42	34	**34**
34P	146	167	167	205	205	31	204	185	171	**171**	115	-37	-18	34	**34**
35C	99	67	162	375	50	100	233	249	227	64	-1	-166	-87	148	-14
35P	122	250	225	363	149	249	322	294	125	195	-127	-72	-69	238	-46
36C	145	509	282	313	253	199	360	179	56	55	-54	149	103	257	198
36P	125	280	167	285	171	118	386	151	328	176	7	-106	16	-43	-5
37C	88	133	67	100	67	176	223	305	49	51	-89	-90	-238	51	16
37P	185	454	167	91	74	50	508	247	176	121	135	-54	-80	-85	-47
38C	73	77	92	55	80	135	69	38	41	32	-62	8	54	14	48
38P	239	175	16	45	58	209	110	39	11	35	30	65	-23	34	23
40C	86	167	67	133	133	44	183	57	140	76	42	-16	10	-7	57
40P	167	223	152	300	117	432	75	97	40	38	-265	148	55	260	79
42C	152	158	600	200	222	200	101	389	154	76	-49	57	211	46	146
42P	179	167	242	126	127	176	67	170	187	49	2	100	72	-62	78
44C	23	133	67	0	0	88	263	121	33	29	-65	-130	-54	-33	-29
44P	143	200	0	0	0	264	144	0	35	**35**	-121	56	0	-35	**-35**
45C	100	109	151	53	88	218	36	39	0	280	-118	73	112	53	-193
45P	185	150	318	217	0	262	349	407	0	132	-77	-199	-89	217	-132
47C	100	200	167	36	178	178	350	475	0	180	-78	-150	-308	36	-2
47P	172	218	240	200	0	203	190	0	399	0	-31	28	240	-199	0
48C	192	308	294	100	0	68	405	0	78	45	124	-97	294	22	-45
48P	308	0	0	0	0	328	0	111	0	70	-20	0	-111	0	-70
49C	250	250	50	258	250	308	301	114	33	343	-58	-51	-64	225	-93
49P															
50C	159	115	169	282	46	299	161	224	173	116	-140	-46	-55	109	-70
50P	313	146	185	0	55	164	111	167	160	120	149	35	18	-160	-66
26P	77	367	267	333	433	141	604	353	325	377	-64	-237	-86	8	56
Mean C	**166**	**235**	**193**	**177**	**124**	**173**	**254**	**188**	**136**	**124**	**-7**	**-18**	**5**	**41**	**1**
Mean P	**209**	**266**	**211**	**166**	**104**	**227**	**238**	**198**	**155**	**129**	**-18**	**28**	**13**	**11**	**-25**

Table 13A. Plasma renin activity (PRA) and aldosterone (ALDO) in 18 men12 hr before (C12), just before (A0) and after 1, 6 and 12 hr of altitude exposure.

	PRA					ALDO				
Subj. #	**C12**	**A0**	**A1**	**A6**	**A12**	**C12**	**A0**	**A1**	**A6**	**A12**
0	1.67	**2.33**	1.96	1.10	1.07	92	**219**	162	**327**	61
1	0.32		0.48	0.25	0.25	52		86	47	48
3	0.55		0.87	0.71	0.70	81		181	47	47
5	0.48		0.65	0.39	0.34	60		47	69	34
7	0.48		0.43	0.46	0.24	109		81	86	83
9	0.33		0.29	0.23	0.24	53		83	55	50
10	1.49		1.54	**1.35**	1.16	76		42	**97**	152
12	0.25		0.42	0.28	0.23	65		80	63	51
14	0.47		0.62	0.73	0.45	53		87	66	81
15	0.25	0.38	0.35	0.63	0.30	71	67	56	63	30
17	0.93	1.60	1.60	1.14	0.89	147	128	125	63	75
19	0.67	0.71	0.99	0.50	0.64	107	158	176	54	39
20	0.38	0.48	0.79	0.65	0.55	21	31	25	22	52
22	1.36	1.23	1.41	1.62	0.82	136	317	249	152	88
24	0.65	1.23	0.87	0.51	0.51	88	177	90	59	48
25	0.36	0.45	0.45	1.30	0.33	31	90	42	48	35
27	0.31	0.30	0.30	0.29	0.24	29	58	54	25	29
28	0.37	0.43	0.51	0.31	0.38	23	64	38	28	26
Mean	**0.63**	**0.91**	**0.81**	**0.69**	**0.52**	**72**	**131**	**95**	**76**	**57**
vs.C12		**0.046**	**0.001**	0.41	**0.035**		**0.017**	**0.033**	0.77	0.11

Table 13B. Plasma renin activity (PRA) and aldosterone (ALDO) in 21 menstrual cycle women 12 hr before (C12), just before (A0) and after 1, 6 and 12 hr of altitude exposure.

	PRA					ALDO				
Subj. #	C12	A0	A1	A6	A12	C12	A0	A1	A6	A12
2F	0.37		0.38	0.34	0.36	38		48	31	30
2L	0.56		0.99	0.44	0.54	117		260	122	63
4F	0.55		0.41	0.30	0.28	44		54	237	30
4L	0.35		0.32	0.61	0.52	88		116	207	90
6F	0.52		0.84	0.68	0.62	37		77	39	28
6L	0.70		0.90	0.90	1.17	45		105	66	40
8F	0.32	0.57	0.36	0.22	**0.22**	43	52	82	39	**39**
8L	0.30		0.46	0.37	**0.37**	28		170	152	**152**
13F	0.52		0.59	1.31	0.47	33		49	48	23
13L	1.14	1.06	0.92	1.65	1.23	187	244	117	145	94
16F	0.40	0.50	0.52	0.58	0.44	40	155	51	149	43
16L	3.71	2.39	2.11	2.13	2.10	78	304	177	75	59
18F	0.44	0.38	0.25	0.48	0.25	66	194	69	83	39
18L	0.53	0.66	0.53	0.81	0.44	79	263	124	121	43
21F	0.43	0.41	0.35	0.31	**0.31**	31	100	57	59	**59**
21L	0.56	1.11	1.18	0.70	0.37	100	286	108	160	144
29F	0.35	0.59	0.32	0.36	0.29	29	102	28	24	16
29L	4.13	3.12	3.20	2.94	1.99	130	206	60	92	55
30F	0.15	0.21	0.20	0.17	0.13	29	67	48	48	20
30L	0.31	0.59	0.30	0.61	0.22	41	124	99	258	38
31F	0.34	0.54	0.45	0.35	0.39	100	87	58	45	65
31L	0.66	0.89	0.79	0.63	0.58	49	110	58	52	103
37F	0.57	0.75	0.48	0.71	0.38	53	118	125	121	24
37L	1.19	2.28	2.09	1.62	0.93	197	685	352	197	225
38F	0.26	0.44	0.33	0.26	0.22	42	212	163	179	284
38L	0.42	0.66	0.70	0.66	0.55	267	386	121	49	219
39F	0.20	0.41	0.25	0.17	**0.17**	40	118	109	85	**85**
39L	0.38	0.52	0.31			73	212	124		
41F	0.43	0.50	0.45	0.37	0.28	67	67	89	60	97
41L	0.80	1.19	1.38	0.79	0.19	67	376	153	228	37
43F	0.79	0.77	0.63	0.51	0.56	48	73	62	56	44
43L	1.38	1.22	1.66	1.62	1.11	171	256	138	408	119
44F	0.58	0.49	0.78	0.44	0.19	61	94	44	63	2
44L	0.89	1.06	0.80	0.54	0.55	43	171	65	40	36
45F	0.32	0.32	0.25	0.23	0.23	24	84	46	41	54
45L	0.51	0.75	0.49	0.43	0.45	29	129	63	82	95
46F	0.22	0.38	0.20	0.23	0.15	46	185	91	76	71
46L	0.43	1.12	0.43	0.46	0.31	90	178	85	67	74
11F	0.39		0.45	0.42	0.34	38		81	40	35
11L										
23F	0.41	0.52	0.72	0.58	0.65	45	161	61	36	47
23L										
Mean F	**0.41**	**0.49**	**0.44**	**0.43**	**0.33**	**46**	**117**	**71**	**74**	**54**
F vs. C12		**0.003**	0.31	0.65	**0.016**		**<0.001**	**0.003**	**0.030**	0.52
Mean L	**1.00**	**1.24**	**1.03**	**0.99**	**0.75**	**99**	**262**	**131**	**140**	**94**
L vs. C12		0.51	0.79	0.78	0.08		**<0.001**	0.09	0.13	0.60
F vs. L	**0.027**	**0.001**	**0.002**	**0.002**	**0.002**	**0.004**	**0.003**	**0.001**	**0.028**	**0.012**

Table 13C. Plasma renin activity (PRA) and aldosterone (ALDO) in 21 women taking OCPs 12 hr before (C12), just before (A0) and after 1, 6 and 12 hr of altitude exposure.

	PRA					ALDO				
Subj. #	**C12**	**A0**	**A1**	**A6**	**A12**	**C12**	**A0**	**A1**	**A6**	**A12**
4C	0.55	0.93	0.70	0.53	0.56	43	277	125	74	33
4P	1.08	1.46	1.48	1.15	0.94	49	337	128	139	80
6C	1.09	3.72	1.90	2.32	1.39	36	231	92	125	53
6P	4.77	7.81	5.83	5.21	5.73	70	215	111	27	49
16C	0.85	0.45	0.78	0.81	0.86	46	158	50	63	69
16P	1.85	1.82	1.60	2.06	1.52	80	310	78	403	41
21C	1.03	0.99	0.84	0.48	0.50	59	125	101	24	31
21P	2.30	2.94	2.06	2.42	0.95	34	154	139	85	25
29C	2.35	2.51	2.57	2.36	1.84	36	107	36	25	30
29P	3.68	3.36	2.79	2.96	2.89	61	72	30	20	30
32C	0.97	1.59	1.45	0.70	0.47	165	525	130	76	66
32P	0.63	1.06	0.70	0.62	0.64	54	227	155	69	64
33C	0.55	0.42	0.35	0.35	0.23	244	229	105	25	71
33P	0.88	1.06	0.80	2.17	0.82	156	350	184	61	69
34C	0.17	0.19	0.20	0.15	**0.15**	28	98	50	28	**28**
34P	0.96	2.42	1.42	1.06	1.06	35	243	126	47	43
35C	1.32	1.35	1.74	1.22	0.76	160	313	110	94	39
35P	1.58	2.25	1.81	3.84	1.81	76	253	96	154	53
36C	0.49	0.41	0.31	0.35	0.22	65	264	119	47	196
36P	1.46	1.41	0.87	1.00	0.60	76	373	243	69	59
37C	2.81		2.56	1.93	2.09	42		63	35	21
37P	3.89	3.54	6.27	2.71	2.43	38	173	103	19	14
38C	3.55	4.50	3.02	2.56	2.02	29	345	151	61	29
38P	5.97	6.86	5.02	5.53	4.91	144	307	177	148	19
40C	0.67	0.67	0.50	0.72	0.57	63	361	99	216	83
40P	1.29	1.80	1.57	1.02	1.06	84	814	225	158	170
42C	1.05	1.02	0.76	0.94	0.71	20	112	42	32	36
42P	0.91	1.03	0.86	0.66	0.67	33	60	27	31	12
44C	5.01	4.25		4.52	2.94	88	182		33	25
44P	10.15	10.44	10.14	9.85	10.56	75	341	151	106	59
45C										
45P	4.76	3.97	4.66	4.40	3.61	137	199	57	94	101
47C	3.79	2.73	4.42	3.32	3.38	200	432	535	195	200
47P	2.50	1.12	1.87	1.72	1.47	216	249	121	117	101
48C	0.94	1.26	0.79	0.60	1.19	40	174	75	76	99
48P	2.92	3.22	4.04	3.16	3.42	61	251	126	94	57
49C	2.88	3.21	2.36	2.12	2.05	19	45	21	20	27
49P	6.42	6.12	4.05	3.75	3.59	98	158	62	32	15
50C	2.92	2.71	2.82	4.85	2.67	19	89	22	37	21
50P	6.10	8.47	5.74	5.31	5.40	145	408	186	25	33
26C										
26P	1.07	1.47	1.38	1.66	1.15	49	308	112	176	51
Mean C	**1.74**	**1.83**	**1.56**	**1.62**	**1.29**	**74**	**226**	**107**	**68**	**61**
C vs. C12		0.42	0.95	0.47	**0.004**		**<0.001**	0.14	0.73	0.41
Mean P	**3.10**	**3.51**	**3.09**	**2.96**	**2.63**	**84**	**276**	**126**	**99**	**55**
P vs. C12		0.07	0.96	0.51	**0.018**		**<0.001**	**0.010**	0.50	**0.015**
C vs. P	**0.001**	**0.002**	**0.008**	**0.001**	**0.009**	0.50	0.16	0.45	0.21	0.45

Table 14A. Atrial natriuretic peptide (ANP) and antidiuretic hormone (ADH) in 18 men 12 hr before (C12), just before (A0) and after 1, 6 and 12 hr of altitude exposure.

	ANP					ADH				
Subj. #	**C12**	**A0**	**A1**	**A6**	**A12**	**C12**	**A0**	**A1**	**A6**	**A12**
0	26.3	22.1	32.8	28.2	26.6	2.37	3.23	2.47	2.48	4.38
1	38.9		63.9	56.6	43.6	1.34		1.57	2.00	1.87
3	13.4		42.1	26.8	27.5	1.59		1.02	1.74	1.48
5	5.9		8.9	8.3	11.0	1.98		2.28	3.21	3.06
7	21.9		47.1	14.2	15.3	2.19		2.30	1.95	1.98
9	18.5		16.7	68.8	16.3	2.07		1.91	3.70	2.05
10	8.7		9.2	**6.3**	3.4	2.45		2.33	**5.89**	9.44
12	35.8		5.8	17.2	5.8	2.67		3.07	4.04	3.41
14	17.7		38.0	12.3	21.1	2.31		3.29	3.75	4.87
15	19.9	10.2	13.3	14.8	28.0	1.19	1.87	1.50	3.95	1.40
17	11.6	24.4	5.7	11.3	14.1	0.94	1.65	1.65	1.26	1.61
19	7.0	3.8	14.1	24.8	4.9	1.63	1.71	1.81	2.36	1.58
20	12.7	19.2	63.3	7.9	5.7	2.41	2.14	3.16	2.53	9.40
22	29.4	12.5	12.9	10.5	6.4	1.68	1.83	1.62	1.51	2.10
24	5.0	18.0	12.4	33.1	14.1	2.01	3.15	2.20	5.48	3.46
25	2.7	5.8	8.9	8.5	24.0	1.30	1.86	2.43	1.80	2.00
27	28.5	31.2	53.8	79.2	20.9	1.32	1.60	0.60	0.39	1.60
28	14.1	35.4	12.5	86.3	8.4	2.81	2.55	2.45	3.85	4.19
Mean	**17.7**	**18.3**	**25.6**	**28.6**	**16.5**	**1.90**	**2.16**	**2.09**	**2.88**	**3.33**
vs. C12		0.50	0.09	0.08	0.69		**0.028**	**0.12**	**0.004**	**0.012**

Table 14B. Atrial natriuretic peptide (ANP) and antidiuretic hormone (ADH) in 21 menstrual cycle women12 hr before (C12), just before (A0) and after 1, 6 and 12 hr of altitude exposure.

	ANP					ADH				
Subj. #	**C12**	**A0**	**A1**	**A6**	**A12**	**C12**	**A0**	**A1**	**A6**	**A12**
2F	21.9		30.0	13.9	18.3	2.00		1.23	1.56	1.45
2L	10.1		8.7	17.9	16.3	2.25		1.32	1.79	1.63
4F	15.9		31.2	11.1	12.5	2.03		1.10	33.02	3.05
4L	17.0		14.1	21.9	7.2	1.87		1.75	6.65	8.44
6F	12.9		21.2	13.1	14.1	1.99		1.87	2.46	2.10
6L	10.6		24.6	12.7	6.6	2.30		1.97	1.65	2.29
8F	11.4	19.2	99.2	16.4	**16.4**	2.24	1.76	2.72	3.73	**3.73**
8L	8.2		12.4	21.3	**21.3**	2.48		11.48	9.76	**9.76**
13F	20.1		15.3	19.0	20.0	3.46		2.09	3.17	3.80
13L	28.3	26.9	40.7	30.9	41.5	2.97	2.90	2.01	3.32	2.48
16F	22.0	25.7	28.7	24.7	17.1	1.88	2.19	2.29	13.80	2.19
16L	34.0	26.8	26.6	36.7	28.6	4.35	4.52	3.20	3.59	3.80
18F	7.8	10.1	53.5	12.0	18.2	1.82	1.51	0.88	2.15	1.69
18L	60.9	31.7	21.7	25.0	22.1	2.01	1.23	1.35	1.74	1.91
21F	12.7	16.6	10.9	14.2	**14.2**	1.70	9.75	7.70	40.21	**40.21**
21L	10.9	7.2	31.6	11.5	45.0	2.21	2.45	1.96	3.24	11.74
29F	12.1	19.2	69.3	24.0	8.4	1.46	1.08	1.05	1.44	0.88
29L	22.9	35.4	41.3	28.9	36.2	3.41	3.30	4.01	2.28	1.57
30F	32.6	5.4	60.0	137.3	174.5	2.19	1.57	1.07	1.15	1.42
30L	17.6	11.8	119.2	28.3	24.4	1.21	1.30	1.18	5.69	1.73
31F	29.4	39.3	31.5	32.8	34.1	1.92	2.52	2.03	2.58	3.07
31L	21.3	8.9	76.1	11.9	13.3	1.44	1.55	0.22	1.32	2.95
37F	63.2	54.2	61.3	65.1	53.0	1.73	2.58	2.84	2.30	2.28
37L	53.8	42.6	41.8	45.4	50.1	1.38	1.49	1.99	2.29	2.90
38F	60.3	56.9	92.7	153.9	153.9	2.25	2.57	54.08	11.00	11.71
38L	36.3	50.0	47.8	72.1	77.4	1.44	1.44	1.17	1.46	4.95
39F	65.9	58.2	67.7	72.8	**72.8**	2.87	3.79	7.97	14.53	**14.53**
39L	64.5	56.8	61.9			4.35	3.06	6.42	21.29	7.65
41F	43.9	34.3	49.1	36.1	36.8	2.07	1.52	1.16	6.63	7.73
41L	27.5	32.0	40.4	36.8	20.3	1.56	1.74	1.34	1.90	4.82
43F	39.3	45.7	37.1	42.1	45.0	1.67	1.40	1.99	2.24	2.14
43L	32.9	29.4	29.2	27.0	41.1	2.17	2.55	1.95	4.79	3.02
44F	40.6	32.7	39.0	43.7	15.7	2.13	1.60	1.58	2.53	2.13
44L	51.1	38.2	59.3	44.7	39.4	2.20	2.83	1.70	2.59	2.19
45F	38.4	17.9	25.2	19.9	36.7	2.13	2.07	1.79	6.66	4.12
45L	33.1	36.2	42.1	43.8	32.9	2.32	2.15	1.93	22.07	2.43
46F	53.9	17.9	54.3	30.8	44.2	1.60	2.22	1.89	2.72	2.54
46L	41.8	25.6	33.4	38.6	30.3	2.05	2.43	2.22	2.27	2.72
11F	7.2		18.0	49.1	14.9	3.87		2.31	2.03	2.36
11L										
23F	11.7	4.3	29.4	22.6	62.0	1.60	1.70	1.70	1.60	1.20
23L										
Mean F	**29.7**	**28.6**	**44.0**	**40.7**	**42.0**	**2.12**	**2.49**	**4.83**	**7.50**	**5.44**
F vs. C12		0.12	**0.013**	0.13	0.16		0.32	0.29	**0.031**	0.10
Mean L	**30.7**	**30.6**	**40.7**	**30.9**	**30.8**	**2.31**	**2.33**	**2.59**	**5.25**	**4.16**
L vs. C12		0.09	0.15	0.54	0.64		0.95	0.60	**0.043**	**0.017**
F vs. L	0.77	0.98	0.48	0.30	0.33	0.23	0.63	0.39	0.30	0.30

Table 14C. Atrial natriuretic peptide (ANP) and antidiuretic hormone (ADH) in 21 women taking OCP's 12 hr before (C12), just before (A0) and after 1, 6 and 12 hr of altitude exposure.

	ANP					ADH				
Subj. #	**C12**	**A0**	**A1**	**A6**	**A12**	**C12**	**A0**	**A1**	**A6**	**A12**
4C	19.3	7.8	20.0	12.9	6.9	2.20	1.85	1.87	20.69	5.67
4P	10.7	5.3	15.9	4.4	28.2	2.05	1.86	1.43	6.19	3.06
6C	50.6	42.5	49.8	51.5	33.6	2.77	3.58	2.44	3.17	5.53
6P	47.8	39.7	44.6	29.5	40.8	2.45	3.21	2.30	3.39	2.17
16C	21.4	10.8	6.2	9.2	29.9	1.97	0.99	0.38	4.75	3.10
16P	21.9	10.3	6.3	7.1	15.0	1.43	1.20	0.51	5.35	1.99
21C	33.0	47.4	39.8	51.6	79.8	3.18	4.12	3.34	5.69	4.36
21P	26.4	30.8	28.9	73.5	43.5	3.19	3.12	3.58	6.96	4.91
29C	7.8	41.5	36.4	39.0	38.3	3.89	3.73	3.31	4.17	3.36
29P	12.2	33.3	16.1	35.6	24.8	3.00	3.66	2.93	2.51	3.12
32C	40.0	42.3	259.0	128.0	374.8	2.85	5.24	2.77	5.03	1.84
32P	180.1	42.3	50.9	39.1	31.1	2.70	2.97	3.00	3.77	10.63
33C	44.7	36.7	56.5	36.4	46.3	5.98	4.14	1.51	1.64	4.66
33P	52.5	36.5	35.4	84.8	60.3	4.07	13.25	2.86	3.98	3.70
34C	55.4	80.2	87.8	48.3	**48.3**	2.49	2.41	1.94	4.73	**4.73**
34P	33.4	24.0	26.1	38.1	28.9	3.24	2.60	2.03	2.22	2.92
35C	42.7	43.7	69.9	38.0	45.5	2.50	2.31	3.40	5.08	2.49
35P	42.1	49.0	62.8	42.6	34.7	3.34	2.31	1.82	26.32	33.17
36C	47.6	48.6	53.3	57.9	70.8	3.82	2.78	2.05	2.29	3.00
36P	49.5	62.9	51.9	68.4	68.4	2.21	2.13	1.45	2.61	2.08
37C	27.4		24.7	31.3	39.0	3.21		3.10	3.05	3.45
37P	31.9	24.3	30.6	31.3	37.2	2.48	2.19	2.63	2.62	3.24
38C	22.6	32.5	27.8	24.3	39.9	3.79	3.30	4.86	2.70	2.71
38P	26.4	26.5	37.0	45.6	52.1	4.16	4.14	3.65	3.85	3.41
40C	32.3	34.6	41.5	45.6	37.3	3.70	2.81	1.98	8.41	3.71
40P	51.9	44.7	62.4	63.5	89.6	2.94	2.19	1.92	6.80	4.67
42C	41.8	29.5	80.2	45.2	67.7	1.57	2.01	2.04	2.58	2.09
42P	44.3	39.8	62.9	44.5	46.7	1.99	1.94	1.90	1.62	2.53
44C	32.1	24.4		24.8	30.7	3.27	3.49	3.68	4.11	3.36
44P	25.1	24.9	37.4	40.7	23.6	3.84	3.51	3.73	4.43	4.28
45C										
45P	28.6	24.9	47.6	26.8	37.0	3.65	3.05	3.62	3.38	7.36
47C	47.9	40.8	53.2	20.2	39.1	3.49	4.11	3.96	3.84	6.68
47P	29.3	43.9	26.5	32.5	49.2	3.73	4.77	4.33	4.63	13.46
48C	61.5	50.5	38.8	78.4	75.9	6.54	4.39	4.94	4.63	6.40
48P	19.7	17.6	61.5	64.1	62.7	3.38	4.02	5.80	5.42	3.38
49C	38.8	35.8	35.3	35.3	34.8	5.60	2.52	2.35	3.30	2.63
49P	30.8	50.8	60.1	63.1	60.5	2.80	2.65	2.72	2.28	2.96
50C	24.3	39.6	24.0	48.3	34.7	5.25	2.04	2.22	3.37	2.44
50P	9.5	29.3	38.3	24.8	29.7	4.79	3.73	2.93	2.31	2.59
26C										
26P	9.3	11.3	27.2	34.9	10.7	2.35	2.61	3.32	2.68	2.23
Mean C	**36.4**	**38.3**	**55.8**	**43.5**	**61.7**	**3.58**	**3.10**	**2.74**	**4.91**	**3.80**
C vs. C12		0.66	0.14	0.22	0.17		0.15	**0.026**	0.24	0.61
Mean P	**37.3**	**32.0**	**39.5**	**42.6**	**41.6**	**3.04**	**3.39**	**2.78**	**4.92**	**5.61**
P vs. C12		0.46	0.76	0.53	0.61		0.46	0.23	0.11	0.10
C vs. P	0.73	0.30	0.22	0.95	0.34	0.05	0.46	0.84	0.88	0.29

Table 15A. Norepinephrine and epinephrine in 18 men
12 hr before (C12) and after 1, 6 and 12 hr of altitude exposure.

	NOREPI				EPI			
Subj. #	**C12**	**A1**	**A6**	**A12**	**C12**	**A1**	**A6**	**A12**
0	207	211	347	204	551	161	31	28
1	301	386	334	325	2	35	20	28
3	142	271	187	85	16	2	0	0
5	104	117	12	63	14	5	15	21
7	632	319	450	427	94	37	21	40
9	248	99	157	273	7	13	32	65
10	97	29	181	230	29	68	20	47
12	326	193	179	184	5	22	35	18
14	299	618	289	330	13	11	24	22
15	658	439	354	131	1	13	20	16
17	480	441	311	348	1	1	16	54
19	225	326	0	251	43	23	50	18
20	297	177	91	29	50	16	39	33
22	183	474	197	134	8	16	0	14
24	203	347	329	367	13	14	48	58
25	83	167	183	176	11	9	39	15
27	310	482	366	222	52	424	164	203
28	172	397	217	225	49	143	220	137
Mean	**276**	**305**	**232**	**223**	**53**	**56**	**44**	**45**
vs. C12		0.49	0.19	0.18		0.92	0.78	0.81

Table 15B. Norepinephrine and epinephrine in 21 menstrual cycle women 12 hr before (C12) and after 1, 6 and 12 hr of altitude exposure.

	NOREPI				EPI			
Subj. #	C12	A1	A6	A12	C12	A1	A6	A12
2F	250	535	299	378	13	1	0	18
2L	226	416	843	414	0	0	0	7
4F	231	167	46	80	2	5	61	13
4L	283	196	195	158	9	12	14	9
6F	182	418	302	252	7	169	5	14
6L	389	360	617	487	9	59	14	32
8F	154	222	172	172	0	5	12	12
8L	217	229	202	202	0	12	15	15
13F	83	253	387	156	11	22	17	14
13L	110	190	288	184	54	6	0	0
16F	118	81	109	141	33	0	50	18
16L	778	1079	864	1009	336	263	339	399
18F	169	120	327	136	14	8	29	19
18L	226	874	758	0	0	3	21	1427
21F	302	404	237	280	91	38	58	118
21L	494	540	323	372	22	244	36	30
29F	31	111	67	78		73		
29L	123	156	138	188	17	22	33	25
30F	73	160	148	110	0	552	90	0
30L	79	315	97	264	501	139	267	169
31F	111	332	270	263	0	347	443	20
31L	380	229	140	206	0		75	56
37F	125	357	202	170		29	35	0
37L	291	218	346	311	4	80	7	67
38F	103	131	99	258	0	116	92	69
38L	193	350	210	157	0	27	34	21
39F	167	281	360	360	48	141	354	354
39L	152	380	239	220	15	54	37	20
41F	220	412	637	354	287			
41L	199	198	318	0			118	0
43F	143	211	231	104	27	222	48	36
43L	219	212	280	406	19	32	36	28
44F	183	238	155	115	46	164	51	20
44L	186	200	249	225	58	302	202	63
45F	787	1127	875	738	601	390	765	705
45L	857	830	964	974	390	376	537	433
46F	716	892	882	813	482	429	401	351
46L	762	906	1200	961	367	487	345	455
11F	88	207	98	113	8	59	6	26
11L								
23F	139	131	140	100	86	144	124	131
23L								
Mean F	**208**	**323**	**288**	**246**	**92**	**146**	**139**	**102**
F vs. C12		**<0.001**	**0.011**	0.06		0.08	**0.050**	0.20
Mean L	**325**	**415**	**435**	**355**	**100**	**124**	**112**	**171**
L vs. C12		**0.044**	**0.040**	0.37		0.56	0.68	0.36
F vs. L	**0.008**	0.31	**0.039**	0.11	0.54	0.70	0.44	0.36

Table 15C. Norepinephrine and epinephrine in 21 women on OCPs 12 hr before (C12) and after 1, 6 and 12 hr of altitude exposure.

	NOREPI				EPI			
Subj. #	C12	A1	A6	A12	C12	A1	A6	A12
4C	25	203	86	94	0	23	20	24
4P	125	173	71	238	0	0	158	760
6C	331	317	221	281	189	144	34	80
6P	176	400	899	1774	46	33	101	864
16C	93	127	96	185	5	10	54	50
16P	166	156	239	86	10	8	52	35
21C	313	500	229	380	17	0	117	28
21P	424	450	221	317	38	24	56	26
29C	80	199	260	207	330	162	142	543
29P	225	209	480	320	166	421	904	139
32C	163	197	140	109	0	54	31	15
32P	74	87	94	198				
33C	70	53	67	67	20	18	0	1
33P	130	425	216	242	428		247	1141
34C	124	222	274	274	386	302		
34P	170	302	347	335	210	98	499	63
35C	178	201	224	217	85	69	49	88
35P								
36C	132	258	174	58	162	353	330	411
36P	153	192	193	201	745	217	1040	93
37C	165	269	191	160	87	126	495	84
37P	954	1400	1361	937	303	299	340	342
38C	309	391	289		32	47	38	
38P	1076	245	218	317	0	35	53	55
40C	143	172	122	225	24	0	57	165
40P	50	264	51	0	0	0	900	123
42C	80	117	139	139		1376		676
42P	96	73			26	0		
44C	339	392	270	292	41	86	124	928
44P	185	366		260	278	82		130
45C	405	1346	265	505	121	347	102	62
45P	1310	1606	2029	1173	329	323	350	472
47C	3139	1908	3764	3809	380	220	423	587
47P	1226	544	739	427	97	100	66	130
48C	174	374	182	313	171	262	43	51
48P	361	322	232	428	45	186	44	46
49C	442	244	197	267	454	162	78	112
49P	221	206	269	239	147	137	234	71
50C	334	336	266	284	143	207	123	95
50P	365	259	292	334	106	35	84	6
26C								
26P	232	340	220	59	6	3	7	10
Mean C	**352**	**391**	**373**	**414**	**139**	**198**	**126**	**222**
C vs. C12		0.64	0.59	0.14		0.92	1.00	0.31
Mean P	**386**	**401**	**454**	**415**	**157**	**111**	**302**	**251**
P vs. C12		0.41	0.65	0.90		0.41	**0.048**	0.32
C vs. P	0.80	0.98	0.77	1.00	0.70	0.22	0.08	0.57

Table 16. Heart rate variability parameters obtained in 13 subjects with high AMSa scores (Sick) and 13 with low scores (nonsick).

NONSICK		C12								A12							
Subj. #	AMSa	mean	S.D.	S.D./mean	LF	HF	LF (nu)	HF (nu)	LF/HF	mean	S.D..	S.D./mean	LF	HF	LF (nu)	HF (nu)	LF/HF
18F	0.6	905	76	8	426	732	37	63	0.58	667	21	3	42	26	62	38	1.62
27	0.7	1270	77	6	338	348	49	51	0.97	989	67	7	357	74	83	17	4.82
29P	0.9	988	69	7	328	546	38	62	0.60	781	47	6	201	114	64	36	1.76
19	0.9	864	65	8	548	274	67	33	2.00	832	44	5	140	121	54	46	1.16
13F	1.2	1096	69	6	481	449	52	48	1.07	878	73	8	255	373	41	59	0.68
6P	1.2	848	44	5	191	104	65	35	1.84	707	35	5	82	48	63	37	1.71
15	1.3	964	81	8	307	127	71	29	2.42	880	46	5	208	95	69	31	2.19
20	1.4	1063	89	8	1373	247	85	15	5.56	820	54	7	584	72	89	11	8.11
17	1.8	1116	109	10	1824	574	76	24	3.18	846	131	15	1793	1226	59	41	1.46
32C	1.9	934	73	8	362	587	38	62	0.62	678	42	6	93	118	44	56	0.79
31F	2.1	974	67	7	286	767	27	73	0.37	816	76	9	516	228	69	31	2.26
46L	2.3	1007	48	5	233	264	47	53	0.88	800	87	11	258	212	55	45	1.22
40C	2.6	949	49	5	133	236	36	64	0.56	725	39	5	21	20	51	49	1.05
Mean	**1.5**	**998**	**70**	**7**	**525**	**404**	**53**	**47**	**1.59**	**801**	**59**	**7**	**350**	**210**	**62**	**38**	**2.22**
S.D.	0.6	115	18	2	498	220	18	18	1.47	91	29	3	466	320	14	14	2.06

SICK		C12								A12							
Subj. #	AMSa	mean	S.D.	S.D./mean	LF	HF	LF (nu)	HF (nu)	LF/HF	mean	S.D.	S.D./mean	LF	HF	LF (nu)	HF (nu)	LF/HF
10	9.8	900	50	6	101	127	44	56	0.80	662	36	5	99	75	57	43	1.32
44F	8.4	811	64	8	382	436	47	53	0.88	644	42	7	110	112	50	50	0.98
45F	9.7	837	60	7	240	226	52	48	1.06	690	74	11	235	163	59	41	1.44
47C	6.4	746	19	3	25	10	71	29	2.50	602	16	3	15	6	71	29	2.50
0	7.7	832	48	6	207	80	72	28	2.59	709	42	6	134	98	58	42	1.37
25	7.7	1145	86	8	496	1121	31	69	0.44	698	90	13	356	636	36	64	0.56
48C	7.3	880	44	5	82	133	38	62	0.62	588	11	2	6	5	55	45	1.20
23F	6.6	949	85	9	500	470	52	48	1.06	631	53	8	104	100	51	49	1.04
9	5.8	1398	66	5	193	227	46	54	0.85	822	45	5	110	153	42	58	0.72
26P	5.7	1111	167	15	5164	989	84	16	5.22	919	117	13	897	1879	32	68	0.48
42P	7.9	829	49	6	175	200	47	53	0.88	549	15	3	20	2	91	9	10.00
16C	5.8	1007	113	11	1091	1104	50	50	0.99	702	19	3	44	7	86	14	6.29
21P	5.7	737	56	8	151	291	34	66	0.52	597	10	2	9	2	82	18	4.50
Mean	**7.3**	**937**	**70**	**7**	**677**	**416**	**51**	**49**	**1.42**	**678**	**44**	**6**	**165**	**249**	**59**	**41**	**2.49**
S.D.	1.4	187	37	3	1377	396	16	16	1.33	101	33	4	242	518	19	19	2.82

CV: coefficient of variation (S.D./mean);

LF: low frequency component of area (variance); HF: high frequency component; nu: normalized unit

Table 17A. T2 values for CSF volume and for splenium and genu regions of corpus callosum from MRIs before and after altitude exposure in 13 sick and 13 nonsick subjects.

					Corpus callosum					
NONSICK		CSF volume (ml)			Splenium (ms)			Genu (ms)		
Subj.#	**AMSa**	**pre**	**post**	**diff.**	**pre**	**post**	**diff.**	**pre**	**post**	**diff.**
18-fol	0.58	160.9	159.5	-1.4	76.3	76.8	0.5	60.2	64.9	4.7
27	0.67	190.6	179.5	-11.1	66.8	63.2	-3.6	63.2	64.8	1.7
2-lut	0.70	133.1	127.4	-5.7	67.3	64.4	-2.9	64.1	63.6	-0.4
3	0.76	141.5	128.3	-13.2	69.8	74.8	5.0	68.3	64.8	-3.5
50-pil	0.88	95.4	82.3	-13.1	70.9	72.4	1.4	63.6	65.0	1.4
19	0.94	234.6	215.6	-19.0	74.3	73.2	-1.1	60.1	60.5	0.4
13-fol	1.15	135.1	128.5	-6.7	75.5	73.2	-2.2	65.7	63.2	-2.5
14	1.18	122.5	106.4	-16.1	78.1	74.7	-3.4	63.5	63.0	-0.6
29-lut	1.19	90.7	87.6	-3.1	74.1	71.6	-2.5	62.6	64.1	1.5
6-lut	1.19	100.8	98.7	-2.1	68.6	74.5	5.9	57.0	58.5	1.5
15	1.26	170.1	162.6	-7.5	72.0	76.9	4.9	64.6	65.1	0.5
20	1.40	103.1	92.8	-10.3	67.0	68.8	1.8	65.9	68.4	2.5
17	1.79	182.9	170.3	-12.6	72.9	70.0	-2.9	62.3	64.0	1.8
Mean	**1.05**	**143.2**	**133.8**	**-9.4**	**71.8**	**71.9**	**0.1**	**63.1**	**63.8**	**0.7**
SD	**0.34**	**43.1**	**41.0**	**5.5**	**3.8**	**4.3**	**3.5**	**2.9**	**2.4**	**2.1**
SICK										
45-fol	9.70	110.1	98.4	-11.7	69.3	69.7	0.4	62.8	62.0	-0.8
42-pla	8.52	108.5	103.5	-5.0	71.8	74.5	2.7	65.4	64.5	-0.8
44-fol	8.37	176.0	167.4	-8.6	66.0	80.4	14.4	57.2	63.1	5.9
34-pla	7.85	159.0	164.9	5.9	68.3	69.5	1.3	57.6	58.8	1.1
25	7.74	152.3	137.5	-14.8	75.8	71.9	-3.9	68.3	63.8	-4.5
0	7.74	227.0	216.9	-10.1	65.4	68.9	3.4	56.9	59.1	2.2
48-pla	7.29	155.7	135.4	-20.3	67.6	64.9	-2.6	58.9	62.2	3.3
39-fol	7.22	108.8	89.1	-19.7	67.1	72.7	5.7	63.5	58.9	-4.6
23-fol	6.63	138.2	125.4	-12.8	70.9	69.1	-1.8	64.0	69.9	5.8
47-pla	6.38	146.1	139.1	-7.0	74.6	67.0	-7.7	62.8	64.1	1.3
41-lut	7.82	98.8	83.8	-15.1	78.0	63.2	-14.8	61.9	74.5	12.6
9	5.77	232.6	228.0	-4.6	88.2	69.8	-18.4	62.9	63.6	0.7
38-fol	10.18	80.4	70.0	-10.4	66.3	72.5	6.2	61.1	60.9	-0.2
Mean	**7.79**	**145.7**	**135.3**	***-10.3***	**71.5**	**70.3**	**-1.2**	**61.8**	**63.5**	**1.7**
SD	**1.23**	**46.5**	**48.9**	**6.9**	**6.4**	**4.4**	**8.8**	**3.4**	**4.4**	**4.6**
All (n=26)										
Mean	**4.42**	**144.4**	**134.6**	***-9.8***	**71.6**	**71.1**	**-0.5**	**62.5**	**63.7**	**1.2**
SD	**3.55**	**43.9**	**44.2**	**6.2**	**5.2**	**4.3**	**6.6**	**3.2**	**3.5**	**3.5**
r vs. AMSa		**-0.08**	**-0.09**	**-0.08**	**-0.14**	**-0.12**	**0.03**	**-0.23**	**-0.09**	**0.12**
P: Sick vs. Non	**<0.001**	**0.89**	**0.90**	**0.70**	**0.87**	**0.36**	**0.64**	**0.28**	**0.80**	**0.48**

Italics: P<0.05 vs. zero

Table 17B. MTC values for CSF volume and for splenium and genu regions of corpus callosum from MRIs before and after altitude exposure in 13 sick and 13 nonsick subjects.

					Corpus callosum					
NONSICK		CSF volume (ml)			Splenium			Genu		
Subj.#	**AMSa**	**pre**	**post**	**diff.**	**pre**	**post**	**diff.**	**pre**	**post**	**diff.**
18-fol	0.58	184.6	206.2	21.5	17.9	17.7	-0.3	18.7	18.2	-0.4
27	0.67	202.6	203.2	0.7	17.7	18.1	0.4	19.1	18.9	-0.1
2-lut	0.70	198.4	180.1	-18.3	17.0	19.0	2.0	17.5	18.9	1.4
3	0.76	159.8	146.1	-13.7	17.5	17.7	0.2	17.9	17.5	-0.4
50-pil	0.88	140.0	117.1	-22.9	18.7	18.3	-0.4	17.7	18.7	1.0
19	0.94	223.2	232.7	9.5	17.3	19.8	2.5	18.3	18.3	0.0
13-fol	1.15	157.7	162.9	5.2	18.3	18.0	-0.3	19.1	18.7	-0.3
14	1.18	152.4	133.1	-19.4	17.4	18.0	0.6	18.3	18.6	0.3
29-lut	1.19	109.3	103.1	-6.1	17.5	17.8	0.3	18.9	18.4	-0.5
6-lut	1.19	125.2	112.9	-12.3	18.1	18.0	-0.1	18.8	18.9	0.1
15	1.26	187.8	186.8	-1.0	18.8	18.7	-0.2	19.4	19.3	-0.1
20	1.40	132.8	125.3	-7.5	17.8	18.1	0.3	18.2	17.8	-0.4
17	1.79	213.5	214.7	1.2	18.2	18.7	0.6	18.9	18.6	-0.3
Mean	**1.05**	**168.3**	**163.4**	**-4.8**	**17.9**	**18.3**	**0.4**	**18.5**	**18.5**	**0.0**
SD	**0.34**	**36.1**	**43.5**	**12.7**	**0.5**	**0.6**	**0.9**	**0.6**	**0.5**	**0.6**
SICK										
45-fol	9.70	125.1	119.6	-5.5	18.1	17.8	-0.2	18.9	19.1	0.1
42-pla	8.52	136.4	124.0	-12.3	17.4	17.6	0.3	18.7	18.2	-0.5
44-fol	8.37	196.5	197.2	0.8	18.4	17.7	-0.8	18.6	18.1	-0.5
34-pla	7.85	185.1	191.1	6.1	17.7	17.9	0.2	18.4	19.3	0.9
25	7.74	179.2	160.5	-18.7	18.0	17.7	-0.4	19.0	18.5	-0.5
0	7.74	236.7	236.7	0.0	18.7	18.4	-0.2	18.5	19.0	0.5
48-pla	7.29	188.9	163.7	-25.2	19.2	17.7	-1.6	18.6	18.8	0.2
39-fol	7.22	131.1	110.7	-20.4	17.9	18.2	0.4	18.8	19.4	0.6
23-fol	6.63	164.3	149.5	-14.8	17.4	18.6	1.2	17.6	18.6	1.0
47-pla	6.38	160.2	122.6	-37.6	18.4	18.7	0.3	16.5	18.9	2.4
41-lut	7.82	142.3	108.9	-33.4	18.1	17.9	-0.1	18.4	18.3	-0.2
9	5.77	225.5	247.0	21.5	16.7	16.3	-0.4	18.7	18.7	-0.1
38-fol	10.18	109.2	90.0	-19.2	18.1	17.3	-0.8	18.1	18.5	0.3
Mean	**7.79**	**167.7**	**155.5**	***-12.2***	**18.0**	**17.8**	**-0.2**	**18.4**	**18.7**	**0.3**
SD	**1.23**	**38.8**	**49.9**	**16.5**	**0.6**	**0.6**	**0.7**	**0.7**	**0.4**	**0.8**
All (n=26)										
Mean	**4.42**	**168.0**	**159.5**	***-8.5***	**17.9**	**18.1**	**0.1**	**18.4**	**18.6**	**0.2**
SD	**3.55**	**36.7**	**46.0**	**14.9**	**0.6**	**0.6**	**0.8**	**0.6**	**0.4**	**0.7**
r vs. AMSa		-0.11	-0.17	-0.26	0.19	-0.36	-0.41	-0.03	0.16	0.13
P: Sick vs. Non	**<0.001**	0.97	0.67	0.21	0.53	0.07	0.06	0.60	0.35	0.29

Italics: P<0.05 vs. zero

Appendix 2

WORKING GUIDELINE FOR EXPERIMENTAL TASKS AND PROCEDURES

DAY 1 (CONTROL)

"Morning Baseline"procedures

6:00 - 6:30 AM	1)Subject voids overnight urine and measures volume 2) Drinks water (and/or breakfast drink) to total 1,000 ml (or as adjusted for sleep time) when added to urine volume 3) Eats standard breakfast and drinks water or juice, etc., in addition, to total 0.5% of body weight. Can have one cup of coffee/tea, if usual, included in the above

Subject reports to the chamber laboratory at 1:00 PM and remains there for the rest of that day

1:00 -3:00 PM	1) Record body weight and attach ECG electrodes 2) Insert venous cannula 3) Venous blood draw, (if female, progesterone only) 4) Practice Symptom scores (LL, ESQ) 5) Practice Cognitive tests twice (9th and 10th) 6) HVR (poik X 2, iso) and 3-breath N_2 and O_2 tests 7) Cold pressor test: measure baseline BP, HR, epi and norepi. Then BP and HR and pain index every min for 5 min and draw sample for epi and norepi during the last min.
3:30-4:00	(1) Void Urine and drink to equal volume (2) Eat snack (3) Record weight (4) Draw baseline for Evans, NaBr and D_2O
4:00	(5) Drink D_2O-NaBr cocktail, record exact time (6) Inject Evans, record exact time (e.g. 4:00 PM)
4:10	Venous blood (Evans), record exact time
4:20	Venous blood (Evans), record exact time
4:30	Venous blood (Evans), record exact time
5:00	Venous blood (Evans), record exact time
5:00 - 6:00	Check stick-on electrodes. Then subject rests quietly, lights out, at basal state for subsequent hormone draw, calibrate and update Consentius metabolic device
6:00-7:00 PM	**<u>"Hour 12:00" Control measurements (C12)</u>** 1) Venous blood (Evans, NaBr, D_2O, 6 hormones, extra plasma, elect, creat, PP, osmol, PD, Hct), record exact time 2) Spirometry 3) Symptoms (LL, ESQ) 4) Cognitive testing

5) Check "record" button on Consentius to record following resp. file
6) Anesthetic for arterial, calibrate and set end-tidals
7) Respiratory measurements (plus end-tidal, BP, HR)
8) Arterial blood
9) "End test" on Cons. and save Cons. file to appropriate HRV directory and rename as "3-breath" for next test
10) 3-breath N_2 test (twice) and 3-breath O_2 (once), record end-tidal cals

(7:00) 11) Venous blood (Evans, NaBr, D_2O) , record exact time
12) Void urine, collect sample, (protein, elect, creat, osmol), and drink ad lib
13) Record weight
14) Record body temp
Remove catheter

(7:15-7:30) **Go to VAMC for baseline MRI**
Symptom scores (LL) after MRI
Prescribed evening meal after MRI

DAY 2 (ALTITUDE CHAMBER)

5:00 - 5:30 AM Subject arrives at chamber with overnight urine (if necessary)
1) Voids over-night urine (volume only)
2) Drinks water (and/or breakfast juice) if needed to total 1,000 ml with urine volume
3) Eats standard breakfast and drinks water or juice, in addition, to total 0.5% of body weight

5:30-6:30 4) Insert venous catheter
5) Venous blood draw (if female-also progesterone) **(A0)**

"Normoxia Baseline" measurements

6:30-6:45 1) Symptoms (LL) **(A0)**
2) Void and drink

6:45-7:00 Enter chamber, ascent to 426 mm Hg (16,000 ft)
1) Set "Time zero" on clock
2) Record weight
3) Record body temp

7:30-8:00 Rest and lights out for subsequent hormone blood draw

"<u>1 hr" measurements at altitude (A1)</u>

8:00-9:00 AM 1) Venous blood (6 hormones, extra plasma, elect, creat, PP, osmol, PD, Hct)
2) Spirometry
3) Symptoms (LL, ESQ)
4) Cognitive testing
5) Check "record" button on Consentius to record following resp. file
6) Anesthetic for arterial, calibrate and set end-tidals
7) Respiratory measurements (plus end-tidal, BP, HR)
8) Arterial blood

9) "End test" on Cons. and save Cons. file to appropriate HRV directory and rename as "3-breath" for next test
10) 3-breath N_2 test (twice) and 3-breath O_2 (once), record end-tidal cals
11) Record body temp

10:00 — 1) Void urine (0-3 hr interval) and collect (protein, elect, creat ,osmol) and drink
2) Record body weight

11:00 AM -12:00 — Lunch Time
12:30-1:00 PM — Rest and lights out for subsequent blood draw

"Hour 6" measurements at altitude (A6)

1:00-2:00 PM — 1) Venous blood (6 hormones, extra plasma, elect, creat, PP, osmol, PD, Hct)
2) Void urine (3-6 hr interval) and collect (protein, elect, creat ,osmol) and drink
3) Record body weight
4) Spirometry
5) Symptoms (LL, ESQ)
6) Cognitive testing
7) Check "record" button on Consentius to record following resp. file
8) Respiratory measurements (plus end-tidal, BP, HR)
9) "End test" on Cons. and save Cons. file to appropriate HRV directory and rename as "3-breath" for next test
10) 3-breath N_2 test (twice) and 3-breath O_2 (once), record end-tidal cals
11) Record body temp

3:30-4:00 — 1) Void urine (6-9 hr interval) and collect (protein, elect, creat, osmol) and drink,
2) Snack time
3) Record body weight
4) Draw baseline blood for D2O, NaBr, Evans
5) Drink D_2O-NaBr cocktail, record exact time
4:00 — 6) Inject Evans, record exact time (e.g. 4:00 PM)
4:10 — Venous blood (Evans), record exact time
4:20 — Venous blood (Evans), record exact time
4:30 — Venous blood (Evans), record exact time
5:00 — Venous blood (Evans), record exact time
5:00 - 5:30 — Check stick-on electrodes
5:30-6:00 — Subject rests quietly, lights out, to be at basal state for subsequent blood draw, calibrate and update Consentius

6:00-7:00 — **"Hour 12:00" Altitude measurements (A12)**
1) Venous blood (Evans, NaBr, D_2O, 6 hormones, extra plasma, elect, creat, PP, osmol, PD, Hct) , record exact time
2) Spirometry
3) Symptoms (LL, VA's, ESQ)
4) Cognitive testing

	5) Check "record" button on Consentius to record following resp. file
	6) Anesthetic for arterial, calibrate and set end-tidals
	7) Respiratory measurements (plus end-tidal, BP, HR)
	8) Arterial blood
	9) "End test" on Cons. and save Cons. file to appropriate HRV directory and rename as "3-breath" for next test
	10) 3-breath N_2 test (twice) and 3-breath O_2 (once), record end-tidal cals
(7:00)	11) Venous blood (Evans, NaBr, D_2O) , record exact time
	12) Void urine (9-12 interval), collect, (protein, elect, creat, osmol) and drink ad lib
	13) Record body temp
	14) Record weight
	Remove catheter
7:00-7:15	Descend to "Albuquerque"
7:15-7:30	**Place subject on 13.7% O_2 and transport to VA Medical Center for MRI**
	1) Symptoms (LL) after MRI
	2) Void urine and collect (volume, protein, creat, elect, osmol), record time after MRI

Appendix 3-A

Presented at 10th International Hypoxia Symposium, Lake Louise, Canada, February 1997.

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CHAPTER 5
WOMEN, EXERCISE, AND ACUTE MOUNTAIN SICKNESS

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Introduction

Acute mountain sickness (AMS) has been studied predominantly in men. However, due to physiological differences between genders (including, but not limited to, ovarian hormones), women may have different physiological responses to altitude than men. This may lead to a different incidence and severity of AMS in women. In this chapter we review the influence of the menstrual cycle, oral contraceptives (OCs), and exercise in women on susceptibility to AMS.

Incidence of AMS in Women and Men

Few researchers have compared the incidence and severity of AMS between women and men, and the results are contradictory. Honigman et al[26] studied 3,158 adults visiting moderate altitude (1900-2500 m) for recreation. Of 1,255 women included in that study, 28% developed AMS compared to 24% of the men ($p<0.01$). In another survey conducted at a higher altitude (~4000 m), Hackett et al[21] studied 278 unacclimatized trekkers in Nepal and noted no gender differences in AMS susceptibility. Similarly, Maggiorini et al[28] studied 466 climbers (17% women) in the Swiss Alps (2800-5000 m). The incidence of AMS symptoms between men (53%) and women (57%) was not different. However, there was a significantly higher incidence of HAPE in men (13%) than in women (<1%). Forty-nine men, but only one woman, had to be air-rescued due to pulmonary edema.

Women at Altitude

The first research at altitude on women was most likely in 1913 when Mabel Fitzgerald rode on horseback through the Colorado Rockies and analyzed alveolar gases of altitude residents.[12] Fitzgerald studied 43 residents, men and women, aged 18 to 70 years at moderate altitudes. She found that P_AO_2 and P_ACO_2 were the same in men and women and that hemoglobin concentration was not uniformly higher at

altitude in women, as it was in men. It was 55 years until the next major investigation of women at altitude. In 1969 Hannon et al[24] examined altitude acclimatization in eight women (19-21 years) who spent the summer working and living on the summit of Pikes Peak (4,300 m). These and other studies form the basis for our limited knowledge of the responses of women to acute and prolonged high altitude exposure.

Menstrual Cycle

Hormonal differences between phases of the menstrual cycle in women may cause variations in response to altitude. The normal menstrual cycle is, on average, 28 days long and consists of two major phases: follicular and luteal. In the follicular stage, ovarian follicular growth occurs, and follicle stimulating hormone (FSH) and luteinizing hormone (LH) are secreted. The developing follicle secretes estrogen in response to FSH and LH which signals the hypothalamus to reduce secretion of FSH and LH. In the luteal phase, progesterone and estrogen are secreted by the corpus luteum. Progesterone also causes swelling and secretory development of the endometrium. Approximately 26 days into the normal menstrual cycle, estrogen and progesterone concentrations decrease sharply and menstruation occurs.

Menstrual Cycle and Ventilation

Of the two phases, the luteal phase may have the most effect on adjustment to altitude because during the luteal phase of the menstrual cycle progesterone levels are markedly elevated and progesterone is a potent ventilatory stimulant. For example, when synthetic progesterone is given as a supplement to men or women ventilation is markedly increased.[39] Increased ventilation upon exposure to altitude is said to be the body's first line of defense on exposure to altitude (Fig. 1).[33,43] Thus, the increase in ventilation caused by high levels of progesterone during the luteal phase might be beneficial for high altitude acclimatization.

When women with complete hysterectomies were given either placebo, 1.25 mg estrogen, 20 mg progesterone, or both estrogen and progesterone together, ventilation was increased with progesterone and when given in combination with estrogen by 7±3% and 12±6%, respectively.[39] Given in combination, the synthetic hormones also increased the hypoxic ventilatory response (HVR) but not when given alone ($p<0.05$). Therefore, if an augmented HVR is necessary for better adjustment to altitude, then women taking OCs may have an advantage when visiting high altitude.

Menstrual Cycle and Fluid Balance

Fluid retention is associated with AMS; it appears that individuals with a strong diuretic response suffer less from AMS than individuals who lack this response (Fig. 1)[4,17,19,20,23,48] The changes in fluid regulating hormones with the normal menstrual cycle are still controversial; however, the results suggest higher levels of arginine vasopressin (AVP), plasma renin activity (PRA), and plasma aldosterone (ALD) during the luteal phase compared with the follicular phase.[5,13,29] Other researchers found no significant differences in these hormones between phases of the menstrual cycle.[10,35] It is clear, however, that if ovulation fails, there is no increase in these hormones.

Sundsfjord and Aakvaag[49] studied PRA and plasma renin substrate (PRS), as well as urinary ALD excretion (UAE), in 18 women. The women were divided into

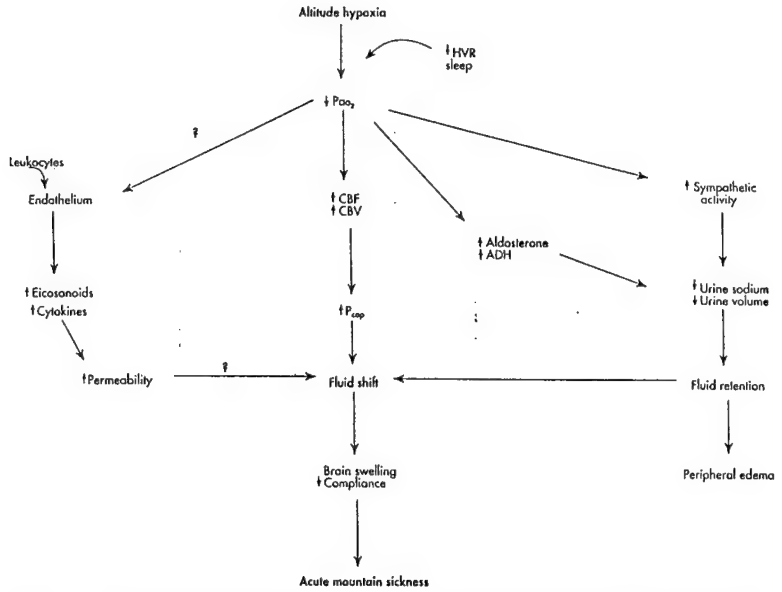

Figure 1 Proposed pathophysiology of acute mountain sickness. HVR, hypoxic ventilatory response; CBF, cerebral blood flow; CBV, cerebral blood volume; Pcap, capillary pressure; ADH, antidiuretic hormone. Reprinted from HACKETT P. H., R. C. ROACH. High-altitude medicine. In: Auerbach P. A., ed. Wilderness Medicine. St. Louis: Mosby, pp. 1-37, 1995.

either a luteal or a luteal-failure group according to their menstrual status. The luteal-failure group showed no significant difference in PRA between the first and second half of the menstrual cycle. However, the luteal group showed a significant increase in PRA during the luteal phase. No difference in PRS between menstrual cycle phases was noted for either group. The UAE rose significantly during the luteal phase in the luteal group, but did not change in the luteal-failure group.

Michelakis et al[29] measured PRA and ALD in six women throughout their menstrual cycles. Five of the 6 women had ovulatory cycles while one failed to ovulate and was considered anovulatory. In the ovulatory cycles both PRA and ALD increased during the luteal phase when progesterone levels were highest. The anovulatory subject had no change in either PRA or ALD throughout her cycle.

Forsling et al[13] studied the variation in the AVP levels throughout the menstrual cycles of eight women. AVP levels were highest at the time of ovulation and lowest at the onset of menstruation. In a later study, Forsling and colleagues[14] studied AVP levels in post-menopausal women given 2 mg/day of estradiol valeriate and/or 10 mg/day of medroxy progesterone (MPA). Estradiol treatment alone resulted in significantly increased AVP levels, while MPA treatment alone had no effect on AVP levels. However, MPA in combination with estradiol treatment resulted in a gradual decrease in AVP levels. The combination treatment most closely mimics the physiology of the luteal phase. During the luteal phase of the menstrual cycle, both

progesterone and estrogen levels are high, thus it seems likely that the combination of these two hormones results in suppression of AVP.

Unlike the studies by Forsling,[14] other researchers have reported no significant differences in AVP levels during the menstrual cycle; however, there are methodological differences that may account for the discrepancies. DeSouza and colleagues[10] found no difference in AVP throughout the cycles of 16 female runners. Eight runners were amenorrheic and eight were eumenorrheic. No difference was found in resting AVP or PRA between the two menstrual cycle phases. However, ALD was significantly greater during the luteal phase in the eumenorrheic runners. The pre-exercise estrogen and progesterone levels for both the amenorrheic and eumenorrheic groups were similar. Thus, as is often the case with physically active women, especially runners, estrogen and progesterone levels can be lower than in their less active counterparts.

Punnonen and others[36] studied AVP changes during the menstrual cycles of 14 ovulatory women. AVP was not significantly different throughout the cycle. However AVP tended to increase at the time of ovulation when estrogen was highest and to fall when progesterone was rising. The failure to find significant differences in AVP levels may be due to not measuring AVP during menstruation when AVP levels are the lowest.[13]

The effect of menstrual status (eumenorrheic versus amenorrheic) on ALD, atrial natriuretic peptide (ANP), and PRA was further studied in a group of women, aged 18 to 37 years.[10] Plasma ALD was found to be lower in the follicular phase than the luteal phase in the eumenorrheic women. In addition, ALD was higher in the eumenorrheic group versus the amenorrheic group during a submaximal exercise test. Before exercise, plasma ANP and osmolality were similar between menstrual cycle phases and between eumenorrheic and amenorrheic groups, but four minutes after exercise ANP was elevated similarly in all groups. Plasma volume changes were similar between groups and no significant relationships existed between plasma ANP or PRA. Progesterone and ALD were positively correlated during the luteal phase of the menstrual cycle. In summary, when a woman travels to altitude during her luteal phase it is unknown whether the high levels of progesterone would be of benefit due to increasing ventilation, or whether they would be detrimental by causing fluid retention and thus rendering her more susceptible to AMS.

Menstrual Cycle and Exercise Performance

Exercise performance may be affected by phase of the menstrual cycle. Schoene et al[47] examined exercise performance between menstrual cycle phases in highly trained eumenorrheic women runners, non-trained eumenorrheic women, and highly trained amenorrheic women runners, aged 17 to 37 years. They compared the effects of menstrual cycle phase in the eumenorrheic women and the effects of training status in all women. They measured the HVR, hypercapnic ventilatory response (HCVR), exercise $\dot{V}_E/\dot{V}O_2$ and $\dot{V}O_{2max}$. The eumenorrheic women had significant increases in resting ventilation and HVR during the luteal phase, with a higher HVR in the eumenorrheic athletes compared to the non-athletes. The amenorrheic group had no differences in HVR from the highly trained eumenorrheic women. The HCVR was higher in the luteal phase for the eumenorrheic athletes but not for the non-athletes. Also in the eumenorrheic women, the non-athletes had a greater exercise performance during the follicular phase versus the luteal phase, while there was

no change in performance in the eumenorrheic athletes. The $\dot{V}_E/\dot{V}O_2$ was greater in the luteal phase for all eumenorrheic women during the entire exercise protocol. The mechanism of the increase in ventilation during the luteal phase is not known.

The possible relationship between increased ventilatory response and reduced exercise performance has also been examined.[6] Ten untrained men (age 27 years) were given ten milligrams medroxyprogesterone acetate (MPA) or placebo before an exercise test in a double-blind study. Each subject performed a $\dot{V}O_{2max}$ test under the influence of MPA or placebo. HCVR was unchanged, resting P_aCO_2 was reduced, and resting pH was increased with MPA administration. Exercise blood gases were similar between groups. Blood lactate increased and bicarbonate decreased more in the MPA group than the control group ($p<0.05$). There was no overall effect on cardiovascular function with MPA, and no difference between MPA and control in $\dot{V}O_2$ for a given workload. Maximal exercise performance as measured by $\dot{V}O_{2max}$, maximum workload, and perceived exertion did not change with MPA treatment. During submaximal performance, $\dot{V}_E$ increased only at 33 and 50 percent $\dot{V}O_{2max}$. When related to absolute carbon dioxide output rather than relative oxygen uptake, $\dot{V}_E$ with MPA was increased at all workloads. The authors suggested there may be a greater effect of MPA during endurance exercise and that their results were similar to studies of women in their luteal phase. However, MPA has 15 times the progestational activity of naturally occurring progesterone and may not cause the same hormonal elevation of the *in vivo* control of ventilation.

Regensteiner et al[40] used mild and moderate exercise to manipulate metabolic rate and measured HVR and HCVR. They studied 12 women (23 to 40 years) in their follicular phase and 13 men (22 to 35 years) who were recreational athletes. End tidal PCO_2 and PO_2, $\dot{V}_E$, SaO_2, heart rate and tidal volume were measured. Mild exercise consisted of leg lifts that increased resting $\dot{V}O_2$ by 25%. Moderate exercise increased $\dot{V}O_2$ to approximately four times resting and consisted of cycling at 37 Watts for women and 49 Watts for men on a cycle ergometer. Women had greater ventilatory equivalents for O_2 and CO_2 and tended to have lower end tidal PCO_2 in mild and moderate exercise. Therefore, women had greater alveolar ventilation which could not be accounted for by HVR or HCVR. Resting HVR and HCVR were similar between genders. However, during mild exercise, HVR was greater in men suggesting that they have greater sensitivity to mild changes in metabolic rate.

Oral Contraceptives

Studying women taking OCs offers an opportunity to look at responses to altitude with control over hormonal fluctuations that occur during the normal menstrual cycle. It is unknown whether OCs would make women more or less susceptible to AMS. With oral contraceptive use, the levels of progesterone and estrogen are kept at an elevated level in relation to the follicular phase, and therefore the hormonal status is similar to the luteal phase and may have the risks and benefits during altitude exposure that are associated with the luteal phase of the menstrual cycle. Oral contraceptives consist of synthetic progesterone and estrogen and are taken to prevent ovulation or to regulate menstruation. The levels of estrogen and progesterone are kept constant throughout the cycle with monophasic OCs, but the hormone levels increase progressively with biphasic and triphasic OCs. The presence of these synthetic progesterones and estrogens prevents the secretion of FSH and LH releasing factors from the hypothalamus which normally act on the pituitary

to release FSH and LH.[42] Because of the absence of these gonadotropin hormones, follicular growth and maturation, and ovulation are prevented,[42] ovarian steroid production is inhibited, and the synthetic steroids now maintain the uterus.[42] As occurs with the natural withdrawal of progesterone and estrogen in the last week of a eumenorrheic woman's menstrual cycle, the cessation of OCs in the last seven days of a 28 day cycle causes menstruation to occur.[42]

A concern when studying women who are taking OCs at altitude is that there are many types of OCs and the research comparing the potencies of different OCs is conflicting. One test of potency between OCs is the delay of menses test.[51] In this test, a set of OCs is taken every day. If breakthrough bleeding occurs before the last of the OCs are taken, the test is negative. If no bleeding occurs while the OCs are taken, the test is positive. Swyer[51] used the delay of menses test on women (< 38 years) with normal menstrual cycles taking ethinyl estradiol, a synthetic estrogen, with either norethindrone, norethindrone acetate, ethynodiol diacetate or norgestrel. They found that norgestrel was two to three times more potent then norethindrone while norethindrone was two times more potent than norethindrone acetate and ethynodiol diacetate in the delay of menses test. Dorflinger[11] reviewed several studies on potencies of different OCs and concluded that delay of menses data indicated that norethindrone, norethindrone acetate, and ethynodiol diacetate are equivalent in potency and norgestrel is five to ten times and levonorgestrel is ten to twenty times the potency of norethindrone.

The elevated progesterone levels with oral contraceptive administration may result in higher resting ventilation. The potential effects of oral contraceptive use on ventilation were studied in twelve women aged 21 to 30 years.[32] Vital capacity, tidal volume, resting $\dot{V}_E$, resting $\dot{V}O_2$, forced vital capacity in one second, midmaximal expiratory flow, and $\dot{V}O_{2max}$ were measured prior to starting OCs, and then three and six months after starting OCs. Resting tidal volume increased after oral contraceptive treatment ($p<0.01$). Resting minute ventilation increased at three months of treatment versus before and decreased from three to six months, although these changes were not significant. Exercise ventilation increased over time with use of OCs.

Oral contraceptives may also alter fluid regulating hormones which could contribute to increased or decreased susceptibility to AMS. Huisveld et al[27] studied the effects of OCs and exercise on the renin-angiotensin system in 20 highly trained athletes (10 OC and 10 non-OC) compared to 24 sedentary females (13 OC and 11 non-OC). Women on OCs had suppressed renin angiotensin activity as measured by lower pro-renin and active renin concentrations, but higher renin substrate concentrations. This suppressive effect of OCs on the renin-angiotensin system was potentiated with exercise, suggesting that OCs may provide a protection from development of AMS by preventing fluid retention. However, another study showed no significant differences in renin activity between women using OCs compared to renin activity in days seven to 12 of a normal menstrual cycle in women not using OCs.[9]

Other effects of OCs include increased resting human growth hormone levels, decreased resting blood glucose, increased free fatty acid concentration during mild exercise,[7] increased exercise human growth hormone, and increased reliance on fat and reduced carbohydrate oxidation during prolonged exercise. It is unknown whether these actions of OCs contribute to AMS.

Exercise and AMS

Rapid rate of ascent to altitude increases the severity of AMS.[22] Hackett[16] found that climbers taking less than four days to reach a 4,300 m base camp at Mt. McKinley were more likely to get ill than subjects taking five to 10 days. In this case, the rate of ascent was increased by increasing physical exertion and resulted in greater incidence of AMS. Our personal observations, along with anecdotal reports by others,[15,34,38] suggest that overexertion may be related to the development of AMS. Also, the incidence of AMS is generally lower when subjects passively ascend to high altitude (as in an altitude chamber or by helicopter ascent on mountains) compared to when they exercise to gain altitude.[37] Thus, although prior physical fitness is unrelated to AMS susceptibility,[18,25,26] exertion during ascent may increase the severity of AMS.

Exercise and Ventilation at High Altitude

It is well established that exercise at altitude decreases SaO_2.[8,46,50] West et al[55] reported that six experienced male climbers, aged 23 to 50 years, had reduced SaO_2 from rest to increasing workloads on a cycle ergometer, along with an increased alveolar-arterial oxygen difference at 5,791 m. This suggests that there are diffusion limitations in the lung resulting in a continued fall in the partial pressure of oxygen in mixed venous blood (P_vO_2) and a desaturation of arterial blood.[52,54,55] In young men (21 to 31 years) studied in Operation Everest II, whose fitness ranged from trained to untrained, the alveolar-arterial oxygen difference increased and P_aO_2 was reduced with exercise.[50] Resting and submaximal cardiac output was maintained and P_vO_2 was reduced. The reduction in P_vO_2 and increase in arteriovenous difference was linearly related to $\dot{V}O_2$. This suggests that at a given submaximal $\dot{V}O_2$ at altitude, a given level of $\dot{V}O_2$ was achieved by reducing P_vO_2 instead of increasing cardiac output.[50,53] If exercise does increase AMS symptoms, enhanced arterial oxygen desaturation and decreased P_vO_2 may be among the initiating events.

Ventilation is linked to arterial oxygen desaturation. Schoene et al[44] found a significant negative correlation between HVR and arterial oxygen desaturation at high altitude. Subjects with a brisk HVR were able to reach and sleep at higher altitudes than subjects with a low HVR. They concluded that subjects with a low HVR have a lower P_AO_2 and a higher $PaCO_2$, which shifts the oxyhemoglobin dissociation curve to the right. Under these conditions, hypoxic exercise would facilitate unloading of oxygen from hemoglobin to the tissues, and limit loading of oxygen at the lungs, resulting in decreased SaO_2.

Exercise and Fluid Balance at High Altitude

Exercise at any elevation affects fluid balance as does hypoxia without exercise. Therefore, it is important to understand the dynamics of fluid balance in humans when exercising at high altitudes.

Exercise at sea level increases AVP, PRA, and ALD secretion[1] which could cause fluid retention. During exercise over five days at low altitude, Milledge et al[31] found that five men (23 to 48 years) had increased PRA and ALD activity at the end of every day, with peak values reached on the second or third days. Increased PRA and ALD activity may have directly caused retention of sodium and caused slight leg

edema.

In 18 male mountaineers, Bärtsch et al[2] found that ALD and AVP levels were greater before and after exercise in subjects with AMS than in subjects without AMS, and suggest that the sodium and fluid-retaining effects of the ALD and AVP responses override the renal effects of ANP in AMS.[2] In another study by the same group, fluid homeostasis was examined in 15 healthy mountaineers on a controlled ascent to 4,559 m.[3] PRA, ALD, AVP, and ANP did not change at rest in subjects without AMS. Subjects with AMS had significant weight gain and increased levels of ANP. The positive correlation of ANP and the increase in cross-sectional area of the right atrium,[3] and a decrease in hematocrit suggest that the increase in ANP in AMS may be secondary to fluid retention and an increase in central blood volume.[4]

In addition, nine male soldiers who performed submaximal exercise at sea level, on acute exposure to 4,300 m (after less than two hours at altitude), and during chronic exposure (after two weeks at 4,300 m) had increased levels of ANP while exercising only on acute exposure to altitude, but not while exercising at sea level or during chronic exposure to altitude ($p<0.05$).[41] From these data it appears that the ANP response changes during acclimatization to altitude possibly because of decreases in cardiac output and stroke volume which would reduce atrial stretch and therefore inhibit ANP release. Thus, ANP may increase in subjects secondary to exercise but independent of AMS, and acclimatization to altitude may lead to a reduction in ANP levels. In summary, hypoxia-induced and/or exercise-induced increases in ALD, PRA, AVP and ANP may explain sodium and fluid retention in subjects developing AMS. Further studies are needed to determine the cause and effect relationships between hypoxia, exercise and the hormonal regulation of fluid balance at high altitudes.

Fitness and AMS

Success at altitude is difficult to predict. For example, some successful climbers have augmented HVR upon arrival at altitude while others have blunted hypoxic ventilatory responses.[45] If HVR is critical for successful climbing, then motivation or other factors may lead to the success of the latter group.[45] Sea-level $\dot{V}O_{2max}$ does not seem to predict climbing success, likely because climbing is usually a prolonged submaximal activity.[45] Some have even suggested that a high level of training may be inversely related to climbing success at very high altitudes. For example, in Operation Everest II, two of the most highly trained subjects were removed from the chamber before the end of the study, suggesting more trained subjects may be less tolerant of extreme altitude. Milledge et al[30] studied fitness and AMS in 17 men aged 23 to 55 years. No correlation was found between fitness and AMS. Thus, fitness at sea level does not predict susceptibility to AMS, and very fit individuals may perform suboptimally at very high altitudes. The limited studies on women exercising in hypoxia give no reason to suspect significant differences from men in the relationship of sea level fitness to susceptibility to AMS.

Summary

Though it is tempting to speculate about significant differences between men and women acutely exposed to high altitudes based on the influences of the ovarian hormones, data available to date support only minimal differences in physiologic

responses, and essentially the same susceptibility to AMS. Further studies are currently underway to resolve the roles of gender, the menstrual cycle and oral contraceptives in physiological responses to both acute and prolonged hypoxia.

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Appendix 3-B

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INCREASED PLASMA VOLUME (PV) AT SIMULATED ALTITUDE AND THE ONSET OF ACUTE MOUNTAIN SICKNESS (AMS).

RC Roach, D Maes, K Riboni, C Conn, M Icenogle, J Loeppky. Lovelace Resp Res Inst, Univ NM, Dept Cardiology, Abq, NM and Copenhagen Muscle Research Ctr. DK.

AMS is a syndrome that occurs in people who ascend to high altitude without taking time for proper acclimatization and includes headache, nausea and dizziness. Fluid retention is associated with AMS. However, whether the observed fluid retention is causal or secondary to AMS has not been established. Furthermore, the time course of the retention of fluid and development of symptoms has not been followed in the first 12 hrs of altitude exposure. We hypothesized that fluid retention, in this case demonstrated by an increased PV, would occur in persons who subsequently developed AMS. To test this hypothesis we studied 13 young healthy volunteers (6 men) before and during a 12 hr exposure to simulated high altitude (barometric pressure = 430 mm Hg). We measured PV by Evan's Blue at baseline, and in the last 3 hrs of the 12 hr altitude exposure. Also, at 1 hr altitude exposure, PV change from baseline was estimated by the hematocrit/hemoglobin ratio technique. After 9-12 hrs altitude exposure the change in PV from baseline was positively correlated with AMS symptom score ($r=0.87$, $p < 0.001$). All subjects with a rise in PV from baseline developed marked symptoms of altitude illness. Furthermore, the relationship of the estimated PV change at 1 hr to the measured PV at 12 hr suggests that the mechanism responsible for retaining fluid is set in place early in altitude exposure, and before symptoms are apparent. Thus, it seems likely that fluid retention is not secondary to the development of symptoms in AMS.

Supported, in part, by US Army Med Res Material Cmd, DAMD17-96-C-6127.

Appendix 3-C

Presented at 11th International Hypoxia Symposium, Jasper, Alberta, Canada, March, 1999.

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Best 10 from Poster Session I: Oral Presentations

Chairs: Fabiola Leon Velarde and Rob Roach **Monday, 1 March 1999 Afternoon (1600-1830)**

1748-1754 **Women At Altitude: No Gender Or Menstrual Cycle Effects On Acute Mountain Sickness (AMS) (Poster #9).**

Riboni K.[1], Maes, D.P.[1], J.A. Loeppky, M. Icenogle[2], R.C. Roach[3].

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The incidence of AMS in women (W) is not clear from previous studies. For example, one study reported the same incidence between genders (Hackett, Lancet 2: 1149, 1976), while another reported a higher AMS incidence for W (Honigman, Ann Intern Med 118: 587, 1983). Furthermore, the effects on AMS of the luteal (L) and follicular (F) phase of the menstrual cycle are unknown. We compared symptoms of AMS (Lake Louise score) and arterial oxygen saturation by pulse oximetry (S_PO_2; Criticare 503) at baseline (635 mmHg) and near the end of 12 hr at a simulated altitude of 4800 m (426 mmHg; A12). Volunteers were 17 W (27 ± 4 yr, BSA 1.78 ± 0.32m^2) and 17 men (M: 27 ± 3 yr, BSA 1.96 ± 0.18 m^2). The W were studied twice in random order near the mid-point of F and L, confirmed by serum progesterone levels on the day of study (F = 0.3 ± 0.1 and L = 10.4 ± 3.9 ng/ml, P<0.0001). The mid-follicular phase was used for comparison of AMS and SPO_2 between genders. At altitude, the AMS incidence (Lake Louise score ≥ 3, with headache) was 59% in W and 59% in M (P=NS). Mean AMS scores were 4.1 ± 0.9 and 3.9 ± 0.9 for M and W, respectively. The S_PO_2 was not different between genders (80 ± 7 at A12). In F and L the AMS incidence was 59% and 63%, respectively. Mean AMS scores were also similar between F and L. At baseline and A12, the S_PO_2 was not different between F and L. In conclusion, in a controlled altitude exposure, women and men, and women in the F and L phases of the menstrual cycle had an equivalent incidence and severity of AMS symptoms. Furthermore, S_PO_2 was similar among groups.

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Appendix 3-D

Presented at 11th International Hypoxia Symposium, Jasper, Alberta, Canada, March, 1999.

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Poster Session I — **Monday, 1 March 1999**
Chairs: Fabiola Leon Velarde and Rob Roach — **Afternoon (1600-1830)**

14. Ventilation Differences Between Men and Women and Response to Acute Simulated Altitude (426 mm Hg).

Loeppky JA[1], Riboni K[1], Maes D[1], Conn C[1], Charlton GA[2], Icenogle M[2], Roach RC[3]. Lovelace Respiratory Research Inst[1] and VA Medical Center[2], Albuquerque NM 87108 and New Mexico Highlands Univ[3], Las Vegas, NM 87701.

It has been reported that women, compared to men, have a greater ventilation ($\dot{V}_E$) per CO_2 output ($\dot{V}CO_2$) at rest and a lower $\dot{V}_E$ response to an acute drop in F_IO_2 (HVR), with some variation with menstrual cycle phase (White et al., JAP 54, 874, 1983). We wished to verify these results in more subjects and during early altitude exposure. The $\dot{V}_E$ and blood gases were measured in 17 men (once) and in 17 women twice, in luteal (L) and follicular (F) phase, before and during simulated altitude of 16,000 ft after 1 hr (A1) and during the 12th hr (A12). At baseline (635 mmHg) the mean $PaCO_2$ (and $P_{ET}CO_2$) were significantly lower in women than men by 3 mmHg, which confirms significantly greater alveolar and effective ventilation relative to $\dot{V}CO_2$ in women. Women had the same breathing frequency in L and F, which was significantly higher than in men, resulting in greater deadspace ventilation per $\dot{V}_E$ in women. At altitude these PCO_2 differences between men and women persisted, with $PaCO_2$ falling by 3 and 7 mmHg at A1 and A12, respectively, in both men and women. The $\dot{V}_E$ increased by 28 and 19% at A1 and 33 and 24% at A12 for men and women, respectively. The $\dot{V}_E$ increase in L was significantly greater than in F at A1 only. Relative to metabolic rate ($\dot{V}O_2$), the percentage increases in $\dot{V}_E$ and effective ventilation were the same for men and women (22%). At baseline, A1 and A12, the mean $PaCO_2$ was never more than 2 mmHg above $P_{ET}CO_2$, indicating no $\dot{V}_A/\dot{Q}$ variation between gender, menstrual phase or altitude. The mean PaO_2 was between 43-45 mmHg (SaO_2 between 78.3-80.5 %) at altitude for all, indicating equivalent oxygenation. These results show that, relative to metabolic rate, women have a greater $\dot{V}_E$ and maintain a lower PCO_2 than men at baseline and altitude. However, the early ventilatory response to altitude is the same in women and men. Supported by US Army Med Res Materiel Cmd, DAMD17-96-C-6127.

PURPOSE

To determine whether there are differences in ventilation, pulmonary gas exchange and acid-base status during the early hours of simulated high altitude between men and women and between menstrual cycle phases.

METHODS

Subjects: 17 men, mean age = 27 yr, range: 20-31

mean $\dot{V}O_2max$ = 46 ml/kg, SD = 8

17 women, mean age = 27, range: 21-33

mean $\dot{V}O_2max$ = 37, SD = 8

Men were tested once and women twice, once in luteal phase, during peak blood progesterone (mean = 11.1 pg/ml, range 6.6-20.1) and once in mid-follicular phase (mean progesterone = 0.4, range 0.2-0.7) in random order. The time between the women's two tests averaged 8 weeks.

Protocol: diet and fluid intake were regulated to simulate each individual's regular diet, beginning two days before altitude exposure, until the subject left the altitude chamber. Baseline (control) measurements reported here were made in the afternoon of the control day at the ambient P_B of 635 mm Hg (5,200 ft = 1,585 m). The following day the subjects entered the chamber in the morning and it was decompressed to 426 mm Hg (16,000 ft = 4,880 m) in 10 minutes. Measurements were then made after one hour at simulated altitude and again during the last (12th) hour at altitude. Seven percent of the experiments were curtailed by severe AMS, but never before 7 hours of exposure

Measurements: Ventilation ($\dot{V}_E$) and pulmonary gas exchange were averaged over 5 minutes from an automated breath-by-breath system (ParvoMedics TrueMax 2400, Consentius Technologies, Sandy, Utah) and end-tidal gases were obtained with a mass spectrometer (MGA-1400). Arterial blood was drawn from a femoral artery puncture near the end of the gas collection interval under local anaesthetic and analyzed with a Radiometer (model ABL-520). Alveolar ventilation ($\dot{V}_A$) was calculated from $\dot{V}CO_2$and P_aCO_2. Whole blood base excess (BE) was calculated from P_aCO_2, pH_a, Hb and S_aO_2.

RESULTS

- P_aCO_2 was always lower in women, especially in the luteal phase, and was reduced by the same degree at altitude in the 3 groups
- $\dot{V}_E$ was always lower in women
- after one hour of altitude $\dot{V}_E$ was higher in the luteal than the follicular phase in the women
- the higher breathing frequency in women resulted in a greater anatomical deadspace ventilation and therefore a lower $\dot{V}_A/\dot{V}_E$ than in men
- $\dot{V}_E/\dot{V}O_2$ was always higher in women than men during all measurement times, and increased the same percentage from baseline to altitude
- P_aO_2 and S_aO_2 were similar between men and women at baseline and altitude
- women had a lower BE (bicarbonate) than men at all times, especially in the luteal phase, but the change (ΔBE) at altitude was the same for men and women

CONCLUSIONS

- Women have a lower $\dot{V}_E$ than men at baseline and after 1 and 12 hours at altitude
- per metabolic rate they ventilate more, partially to compensate for the greater anatomical deadspace ventilation induced by the higher breathing frequency, but also to maintain a lower P_aCO_2
- if the early ventilatory response to altitude is expressed as a percentage change of $\dot{V}_E/\dot{V}O_2$ then there is no difference between men and women in either menstrual phase
- women, especially in the luteal phase, have a lower bicarbonate level than men which indicates a chronic "hyperventilation" whereby their alveolar ventilation is elevated relative to $\dot{V}CO_2$
- why these women maintain a lower P_aCO_2 than men is open to interpretation

ACID-BASE AND OXYGENATION

	Baseline			Altitude – 1 hr			Altitude – 12th hr		
	MALE	FOL	LUT	MALE	FOL	LUT	MALE	FOL	LUT
pH_a	7.42	7.42	7.42	7.44	7.45	7.46	7.47	7.48	7.47
P_aCO_2	38.6	36.7	34.9*+	35.7	33.5*	31.1*+	31.3	29.0*	27.8*
Hb-g%	15.3	13.2*	13.7*	15.6	13.5*	13.6*	15.7	13.7*	14.0*
S_aO_2-%	95.3	95.3	95.6	79.6	80.1	80.5	78.3	79.0	78.7
P_aO_2	82	85	84	44	45	44	44	45	43
ΔBE-mE/L	-	-	-	0	-0.2	-0.1	-0.9	-0.9	-1.1
HR-min^{-1}	56	62*	68*+	71	75	79*	76	82*	82*

* : significant difference ($P<0.05$) vs. males

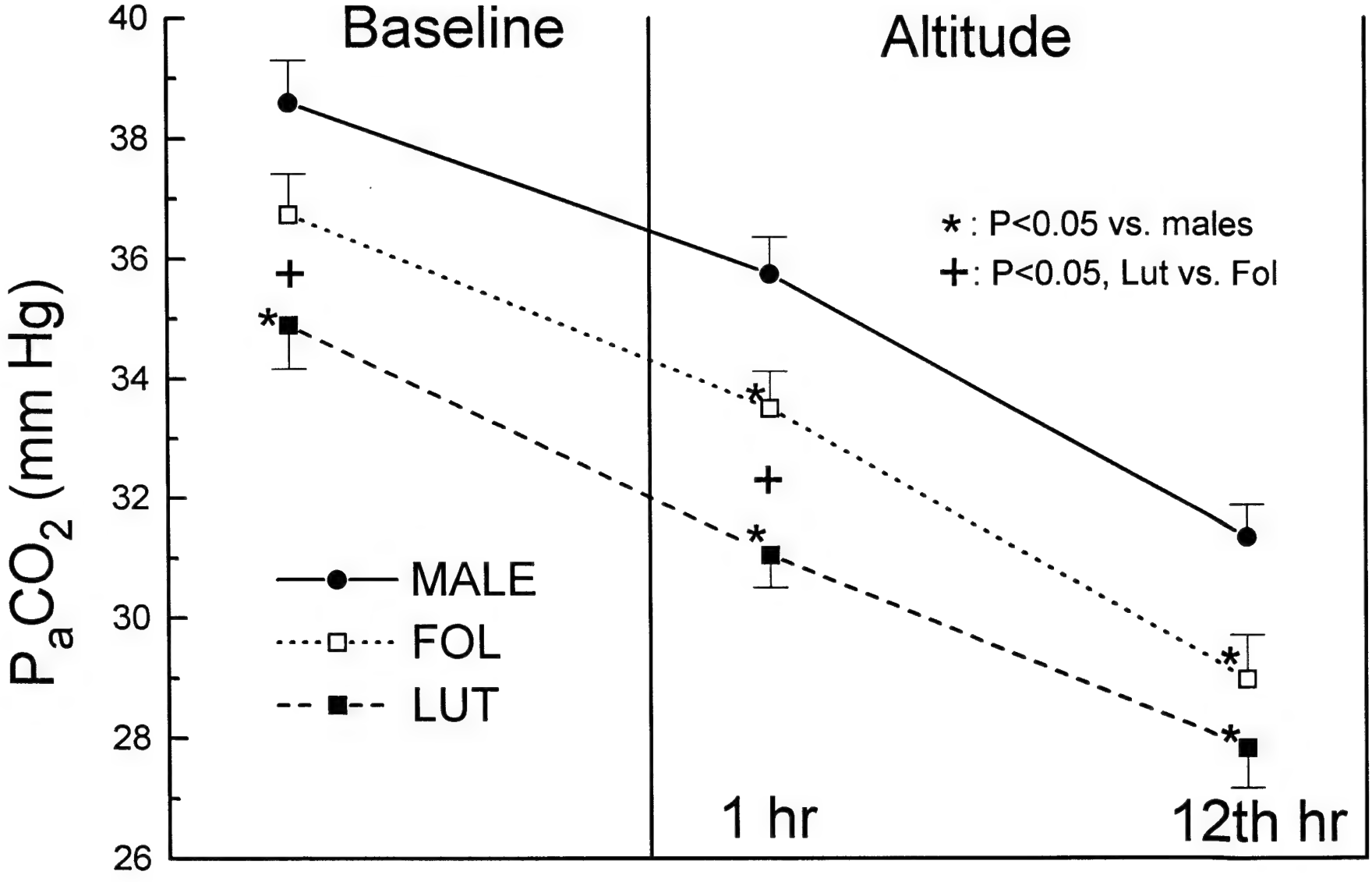
+ : significant difference ($P<0.05$) vs. follicular phase

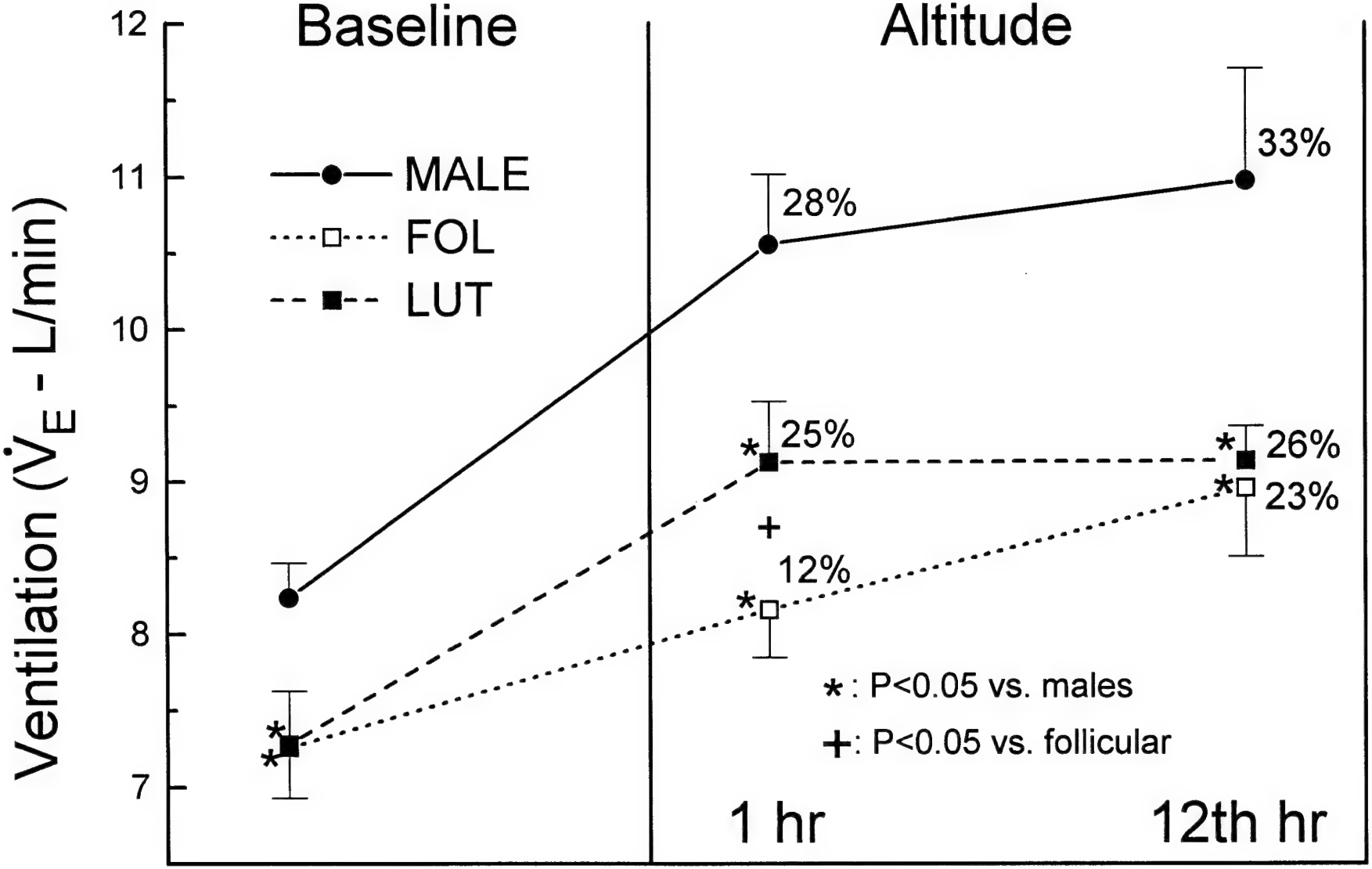
VENTILATION AND GAS EXCHANGE

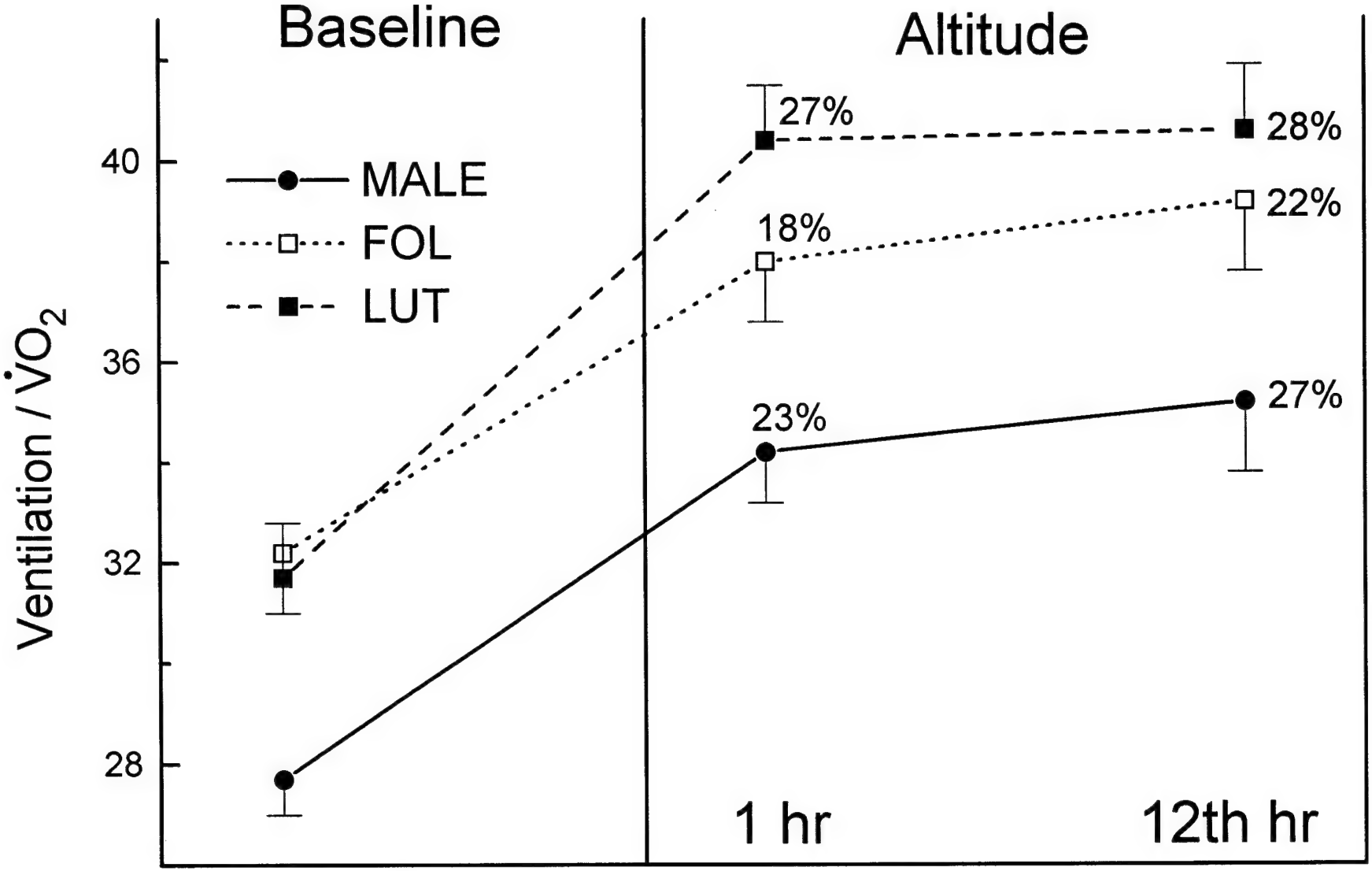
	Baseline			Altitude – 1 hr			Altitude – 12th hr		
	MALE	FOL	LUT	MALE	FOL	LUT	MALE	FOL	LUT
$\dot{V}_E$-L/min	8.2	7.3*	7.3*	10.6	8.2*	9.1*+	11.0	9.0*	9.1*
f_R-min^{-1}	12.6	15.2*	14.9*	14.4	15.2	16.6	15.0	16.2	17.6
V_T-L	0.65	0.48*	0.49*	0.73	0.54*	0.55*	0.73	0.55*	0.52*
$\dot{V}CO_2$-ml/min	247	188*	184*	273	187*	201*	250	179*	174*
R	0.83	0.83	0.80	0.88	0.87	0.89	0.81	0.78	0.77
$\dot{V}O_2$-ml/min	298	227*	230*	310	215*	226*	309	229*	226*
(a-ET)PCO_2	0.7	1.8	0.9	2.0	2.1	0.7*	0.6	0.8	1.3
$\dot{V}_A$-L/min	5.57	4.47*	4.58*	6.59	4.86*	5.59*+	6.91	5.43*	5.43*
$\dot{V}_A/\dot{V}_E$	0.68	0.61*	0.63*	0.63	0.59	0.61	0.64	0.60	0.60

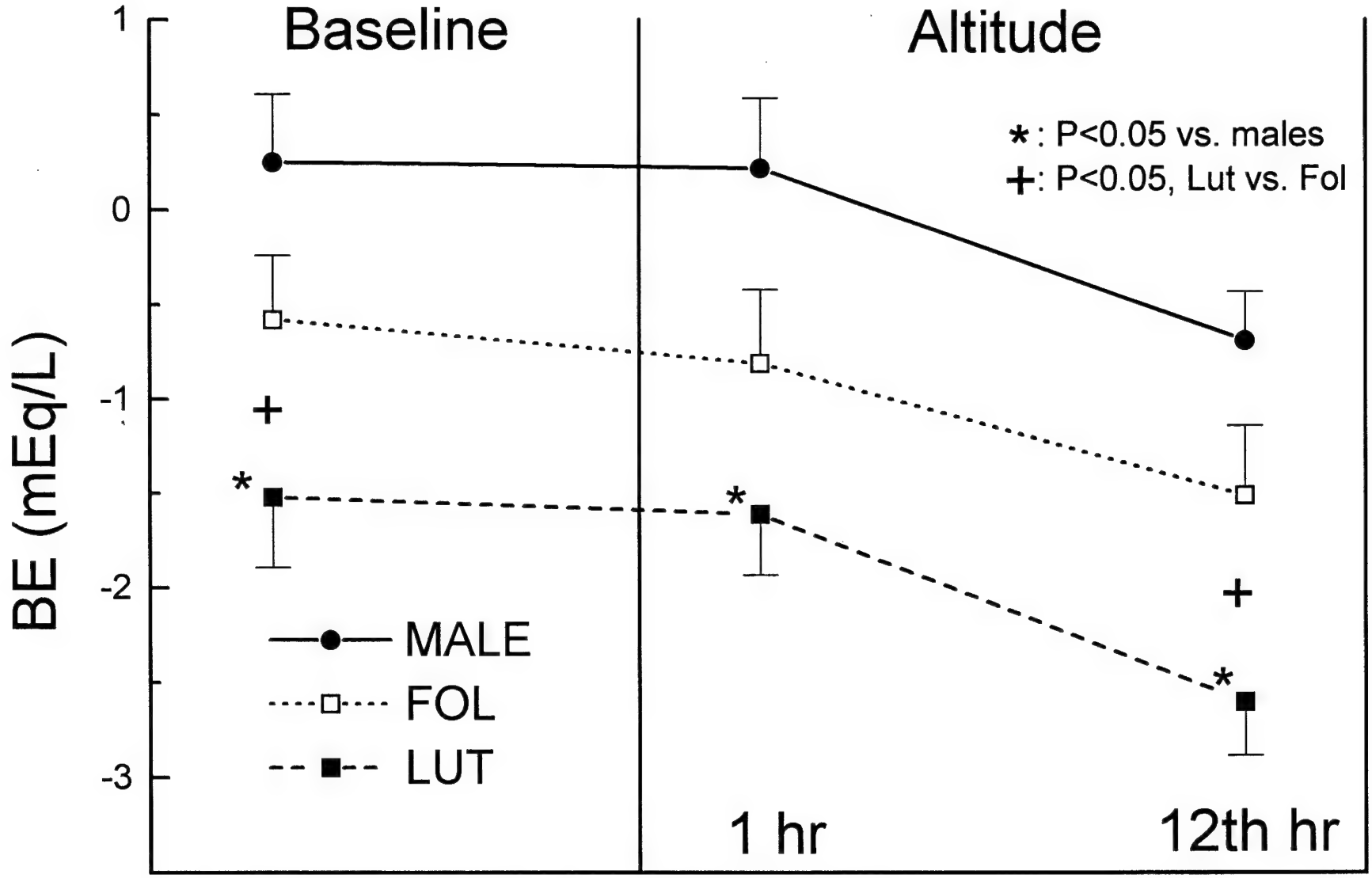
* : significant difference ($P<0.05$) vs. males

+ : significant difference ($P<0.05$) vs. follicular phase


Baseline
Altitude
40
38
36
34
32
30
28
26
P_aCO_2 (mm Hg)
* : P<0.05 vs. males
+: P<0.05, Lut vs. Fol
MALE
FOL
LUT
1 hr
12th hr


Baseline
Altitude
MALE
FOL
LUT
Ventilation ($\dot{V}_E$ - L/min)
12
11
10
9
8
7
28%
33%
25%
26%
23%
12%
*
+
*: P<0.05 vs. males
+: P<0.05 vs. follicular
1 hr
12th hr


Baseline
Altitude
MALE
FOL
LUT
40
36
32
28
Ventilation / $\dot{V}O_2$
27%
28%
18%
22%
23%
27%
1 hr
12th hr


Baseline
Altitude
*: P<0.05 vs. males
+: P<0.05, Lut vs. Fol
BE (mEq/L)
1
0
-1
-2
-3
MALE
FOL
LUT
1 hr
12th hr

Appendix 3-E

Presented at 11th International Hypoxia Symposium, Jasper, Alberta, Canada, March, 1999.

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Hot Topics in Hypoxia

Chairs: Lorna Moore and George Heigenhauser

Tuesday, 2 March 1999
Afternoon (1600-1830)

1730-1745 **Cranial CSF Volume (cCSF) Is Reduced By Altitude Exposure But Is Not Related To Early Acute Mountain Sickness (AMS).**

Icenogle M[1], Kilgore D[2], Sanders J[1], Caprihan A[3], Roach R[4].

VA Medical Center[1], Lovelace Respiratory Research Institute[2], New Mexico Resonance[3], 2425 Ridgecrest Dr SE, Albuquerque, NM 87108 and New Mexico Highlands Univ[4], Las Vegas, NM 87701..

With altitude exposure, there is an increase in cerebral blood flow and intracranial pressure, and a global shift of water into the brain, which may reduce cCSF. One hypothesis is that brain fluid shifts are responsible for AMS. Prior studies have demonstrated the accuracy of T_2 magnetic resonance imaging (MRI) in quantifying cCSF (Kohn et al., Radiology 178: 115, 1991 and Clarke et al., Mag Res Imag 13: 343, 1995). Regional T_2 changes have been described in high altitude cerebral edema (Hackett et al., JAMA 280: 1920, 1998), but little information is available on cCSF changes with acute exposure to altitude or how these changes may relate to early AMS. The goals of our study were to determine 1) if cCSF estimated by T_2 MRI decreased with altitude exposure and 2) if cCSF changes correlated with AMS severity. The T_2 brain images were acquired on 25 subjects (10 males) after 8-12 hours of simulated altitude (426 mm Hg, ~4800 m) and compared with images taken on the preceding control day. Subjects were resting at altitude and diet was controlled with fluid ad lib on both days. The Lake Louise scoring system (LL) was used to serially evaluate AMS and scores for 6th and last hr were averaged. Results showed a control cCSF of 109 ml and a 10 ml reduction in cCSF ($P<0.0001$) after altitude exposure. Twelve subjects with no AMS (mean LL = 0.7, headache = 0.2) and 13 subjects with severe AMS (mean LL = 6.8, headache = 2.6) had similar reductions in cCSF (10.0 vs. 10.4 ml, respectively). Moreover, for all subjects AMS scores were not correlated with the change in cCSF ($r = -0.02$, $n = 25$). Further analyses are necessary to determine if the fall in cCSF during acute altitude exposure was related to regional brain swelling. In summary, T_2 MRI detected acute altitude-induced reductions in cCSF, apparently unrelated to the early stages of AMS. Supported by US Army Med Res Materiel Cmd, DAMD17-96-C-6127.

Appendix 3-F

Presented at 11th International Hypoxia Symposium, Jasper, Alberta, Canada, March, 1999.

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Poster Session II **Wednesday, 3 March 1999**
Chairs: Shigeru Masuyama and Bengt Kayser **Afternoon (1600-1830)**

82. Corpus Callosum (CC) MRI: Early Altitude Exposure.

Kilgore D[2], Loeppky J[2], Sanders J[1], Caprihan A[3], Icenogle M[1], Roach RC[4].

VA Medical Center[1], Lovelace Respiratory Research Institute[2], New Mexico Resonance[3], Albuquerque, NM 87108 and New Mexico Highlands Univ[4], Las Vegas, NM 87701.

Most patients with clinical high altitude cerebral edema demonstrate T2 magnetic resonance imaging (MRI) signal enhancement in the CC which is qualitatively more evident in the splenium than the genu region (Hackett, JAMA 280: 1920, 1998). This is consistent with tissue edema in the CC. Because of these observations, it was postulated that edema in the CC may occur within the first 12 hr at altitude and account for the symptoms of acute mountain sickness (AMS). The goals of our study were to determine if: 1) calculated MRI T2 values (T2 MRI) of the CC increased with acute exposure to simulated high altitude and 2) changes in T2 MRI of the CC correlated with AMS severity. The T2 MRI of the CC was obtained from 25 men and women exposed to 4800m (426 mm Hg) for 8-12 hr. The T2 values in the splenium and the genu of the CC were measured from MRI's started 20 min following altitude exposure and compared with images taken on the preceding control day. During exposure, the subjects were evaluated for AMS by the Lake Louise scoring system (LL). Twelve of these subjects did not have AMS (mean LL = 0.7, range: 0 - 1.5) and 13 had marked AMS (LL = 6.8, range: 5.0 - 9.0), with severe headache. The T2 MRI from the CC increased overall in AMS and non-AMS subjects by 1.2 ms ($P = 0.05$) in the genu and 0.6 ms (NS) in the splenium. Although the average difference (altitude exposure minus control) in T2 MRI from the two regions was greater in AMS than non-AMS subjects (1.1 vs. 0.6 ms), the difference was not significant ($0.5<P<0.8$). There was no significant correlation between AMS severity and the change in T2 MRI from either region (genu: $r = -0.14$, splenium: $r = +0.13$, $n = 25$). Although these results show that acute exposure to altitude was associated with a very small but statistically significant increase in T2 MRI in the genu of the CC, there was no evidence that this change corresponded to the development or severity of AMS.

Supported by US Army Med Res Materiel Cmd, DAMD17-96-C-6127.

Appendix 3-G

Presented at Experimental Biology 99 Meeting, Washington D.C. April, 1999.

Published in the FASEB Journal, vol.13, No. 5, March 15,1999, p A784

WOMEN AT ALTITUDE: GENDER EFFECTS ON ACUTE MOUNTAIN SICKNESS (AMS), VENTILATION, AND OXYGENATION

D.P. Maes, J.A. Loeppky, K. Riboni, M. Icenogle, G.A. Charlton and R.C. Roach. LRRI & VA Med Ctr, Alb. NM, 87108, NM Highlands Univ., Las Vegas, NM 87701. e-mail: dmaes@lrri.org

Incidence of AMS in women (W) is not clear from previous studies. For example, one study reported the same incidence between genders (Hackett, 1976), while another reported a higher incidence for W (Honigman, 1983). We compared symptoms of AMS, resting ventilation [V_E (L/min)and $PaCO_2$ (Torr)] and oxygenation [SpO_2 (%) and PaO_2 (Torr)] in 16 W (27.0±3.8 yr, BSA 1.78±0.32 m^2) and 18 men (M:26.9±3.4 yr, BSA 1.96±0.18 m^2) during 12 hrs at simulated altitude (4800 m; PB = 423 Torr). The W were studied in the mid-follicular phase of their menstrual cycle. Measurements were made before ascent and after 11 hrs at altitude. AMS symptoms were evaluated with the Lake Louise symptom score (LL). The V_E and SpO_2 were recorded for 5 min. At altitude LL was not different between W and M (average scores 4.1±3.7 points). Absolute V_E was less for W than M (W = 8.9±1.8, M = 10.9±3.0; $p = 0.02$) but when expressed for BSA values were not different (W = 5.1±1.2 L/m2, M = 5.6±1.4 L/m2, $p>0.1$). However, $PaCO_2$ was lower for W than M (28.8±3.0 and 31.1±2.5 Torr, respectively; $p<0.05$). SpO_2 was 79.8±7.0 and 79.6±7.0 for W and M, respectively. PaO_2 was 44.6±7.1 and 44.0±5.6 for W and M, respectively. AMS, V_E, and oxygenation were similar between W and M after 11 hrs at altitude. The lower $PaCO_2$ in W may be explained by different breathing patterns, gas exchange efficiency or metabolism. In conclusion, in a controlled simulated altitude exposure, women and men had an equivalent incidence of AMS. Supported, in part, by US Army Med Res Material Cmd, DAMD 17-96-C-6127.

Appendix 3-H

Published in the FASEB Journal, vol.13, No. 5, March 15,1999, p A785

WOMEN AT ALTITUDE: MENSTRUAL CYCLE EFFECTS ON VENTILATION, OXYGENATION AND ACUTE MOUNTAIN SICKNESS (AMS)

Riboni K., D.P. Maes, C. A. Conn, J.A. Loeppky, M. Icenogle, R.C. Roach. LRRI & VA Med Ctr, Albuquerque, NM 87108; New Mexico Highlands Univ, Las Vegas, NM 87701

We hypothesized that in women at altitude the rise in progesterone, a known ventilatory stimulant, from the follicular (F) to the luteal (L) phase of the menstrual cycle would cause a rise in ventilation (V_E, L/min), thus alleviating both altitude hypoxemia and symptoms of AMS. We compared V_E, SpO_2 and AMS symptoms at altitude between F and L in 19 women (mean age: 27 yr). They were studied twice in random order near the mid-point of each phase, confirmed by serum progesterone levels (F=0.3±0.1; L=10.4±3.9 ng/ml, mean±SD, $p<0.001$). Measurements were made in resting supine women after 1, 6 and 11 hrs in a hypobaric chamber (4800 m; 423 mm Hg). Breath-by-breath V_E was averaged over 5 min (ParvoMedics TrueMax 2400). SpO_2 was measured by pulse oximetry (Criticare 503). AMS symptoms were assessed by Lake Louise symptom score. V_E was higher in L than F at 1 hr (9.1±1.6 vs 8.2±1.2, $p=0.04$) and 6 hr (9.7±1.9 and 8.8±1.6, $p<0.06$), but similar values were observed by 12 hr. SpO_2 was similar for F and L, mean 80±1. AMS incidence (Lake Louise score >= 2, with headache) was 79% and 74% in F and L, respectively. Mean peak scores were also similar between F and L. In summary, progesterone and V_E were higher in L during early altitude exposure, but SpO_2 and symptoms of AMS were similar. These findings suggest an initial rise in ventilatory sensitivity in L that subsides by 12 hrs of hypobaric hypoxia. In conclusion, the greater V_E in L during the early hrs of altitude did not protect against hypoxemia or AMS. Supported, in part, by US Army Med Res Material Cmd, DAMD 17-96-C-6127

Appendix 3-I

Presented at American College of Sports Medicine 46th Annual Meeting, Seattle, Washington, June, 1999.

Published in Medicine and Science in Sports and Exercise, vol. 31, No. 5, May Suppl., 1999, p S191

859 SYMPATHOEXCITATION CANNOT ACCOUNT FOR GENDER DIFFERENCES IN EXERCISE- INDUCED ACUTE MOUNTAIN SICKNESS

D.A. Sandoval, D.P. Maes, J.A. Loeppky, M. Icenogle, H.G. Hinghofer-Szalkay, R.A. Robergs and R.C. Roach. ASU, Tempe, AZ; LRRI, Alb. NM; Cntr Exer and Appl Human Physiol, UNM, Alb., NM; Space Med Res Group, Univ Graz, Austria; NM Highlands Univ., LV, NM. e-mail: darleen@asu.edu.

Exercise compared to rest during the first 6 hrs of altitude exposure caused more severe symptoms of acute mountain sickness (AMS) in men (Roach, ACSM 1999). However, in women taking oral contraceptives, exercise had no affect on AMS symptoms (Sandoval, MSSE, 29(5): S135, #778, 1997). We examined catecholamine and adrenocorticotropin hormone (ACTH) responses from these two studies in an attempt to explain the observed gender differences in the effects of exercise on AMS. At simulated altitude (429 mm Hg), we studied 13 subjects, 7 women (W) taking oral contraceptives and 6 men (M), on 2 occasions; once while resting (R), and once while performing 4, 30-min intermittent exercise bouts at 50% maximal altitude workload (EX). AMS symptom scores and plasma levels of norepinephrine (NE), epinephrine (E), and ACTH were measured at 0 and 9 hrs at altitude. Hormone values were log transformed to approximate a normal distribution. AMS scores in EX were significantly greater for M but not for W ($p<0.05$). At rest, NE and E were greater in M vs. W at 0 and 9 hrs (NE=2.6±0.05 and 2.7±0.03 vs. 2.5±0.08 and 2.6±0.06 in M vs. W for 0 and 9 hrs, respectively; E= 1.6±0.06 and 1.8±0.05 vs. 1.4±0.08 and 1.4±0.06, in M vs. W for 0 and 9 hrs, respectively; $p<0.05$). However, EX had no additional affect on NE or E. ACTH did not change over time at altitude, with exercise, or between genders. AMS scores were independent of NE, E, and ACTH. Despite the fact that M, but not W, experienced greater AMS during EX, gender differences in sympathoexcitation occurred independent of exercise and AMS scores. Thus, it is unlikely that sympathoexcitation can directly explain the increased incidence of AMS with EX in men. Further research is needed to clarify these observed gender differences in exercise-induced AMS and sympathoexcitation at simulated high altitude. Supported by NIH Training Grant HL07758

Appendix 3-J

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860 FITNESS AND SUBSEQUENT ACUTE MOUNTAIN SICKNESS IN WOMEN AT SIMULATED HIGH ALTITUDE (4800 M)

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Acute mountain sickness (AMS) occurs in some people after ascent to high altitude. Symptoms of AMS include headache, nausea and dizziness. Although AMS occurs after ascent to altitude which often involves prolonged aerobic exercise, fitness at low altitude when examined in largely male populations does not predict subsequent AMS (Hansen, 1967; Bircher, 1994). However, one study demonstrated lower AMS incidence and severity in those with a high level of aerobic fitness (Gupta, 1978). By studying women and men under a controlled exposure to simulated altitude, we hoped to clarify the role of fitness in subsequent AMS in both women and men. We studied 25 women (age 26.9 ± 3.8 yr) and 18 men (age 26.9 ± 3.4 yr) in an environmental chamber at a simulated altitude of 4800 m (423 mm Hg) for 12 hrs. AMS symptoms were assessed using the AMS-cerebral (AMS-C) component of the Environmental Symptoms Questionnaire and the Lake Louise symptoms score (LL). Symptoms were evaluted before ascent and after 1, 6, and 11 hrs at altitude. On a separate day subjects performed a graded exercise test to volitional exhaustion, and maximal oxygen consumption (VO_2max) was measured. VO_2max was not correlated with peak AMS scores either women (AMS-C $r = -0.18$, $p = 0.40$; LL $r = -0.05$, $p = 0.827$), men (AMS-C $r = -0.35$, $p = 0.16$; LL $r = -0.44$, $p = 0.07$), or for all subjects (AMS-C $r = -0.20$, $p = 0.20$; $r = -0.18$, $p = 0.25$). Maximal ventilation during graded exercise (V_Emax) for all subjects was found to be correlated with resting ventilation (V_E) at 11 hours ($r = 0.32$, $p = 0.05$). Our results indicate that there is no relationship between VO_2max and subsequent susceptibility to AMS for either women or men. The correlation between V_Emax and V_E indicates that there may be a relation to the control of breathing during low altitude exercise and V_E at high altitudes. Supported, in part by US Army Med Res Material Cmd, DAMD 17-96-C-6127

Appendix 3-K

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Comparison of plasma volume changes by Evans Blue and endogenous blood/plasma constituents during acute altitude stress

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Rationale: In order to determine whether a change in plasma volume was correlated with acute mountain sickness (AMS), we exposed 51 subjects (18 men) to simulated altitude at 4,800 m (16,000 ft) in a chamber for 12 hr. Diet and fluid intake were controlled for 3 days before and during the first few hr at altitude. From baseline values obtained at 1800 hr on the control day and final altitude values taken at the same time the next day, the change in plasma volume (Δ%PV) was calculated from 4 **measurements**: (a) Evans Blue (EB), by injecting 12 mg via IV arm catheter and sampling over 2-3 hr with extrapolation of plasma dye concentration to zero time (Linderkamp 1977), (b) total plasma protein concentration (TP) measured within 24 hr, (c) Hb and Hct (HH) measured immediately (no corrections) and (d) plasma density (PD) measured by DMA 58 (thawed samples). The **results** are shown below.

				----------Sign. Diff. \\ r value--------				vs. AMSa	
Meth.	**n**	**Mean**	**SD**	EB	TP	HH	PD	**r**	**P**
EB	98	-6.0	12.2	--------	0.30	0.29	0.20	+0.15	0.15
TP	99	-3.7	5.7	0.055	--------	0.60	0.37	-0.18	0.08
HH	99	-2.9	8.6	0.017	0.24	--------	0.46	+0.09	0.40
PD	93	-3.9	8.0	0.079	0.81	0.30	--------	+0.12	0.24

Discussion: All methods indicated a significant reduction in Δ%PV at altitude. EB had the largest SD and was significantly greater than the other 3 methods (average P=0.05), with the smallest average difference shown by PD (P=0.40). The lowest average correlation coefficient with the other 3 methods was EB (0.26) and the highest was HH (0.46). Values of Δ%PV with TP showed a nearly significant inverse relationship with AMS symptoms, whereas the other 3 methods showed the expected positive correlation, but were non-significant. The variations in results between methods may be the result of inability to control other important variables (ad lib fluid intake, sympathetic tone, vomiting, circulation) in a complicated study with many other measurements. **Conclusion**: The EB method may be the most sensitive to these perturbations and therefore not the best in experiments where environmental stresses cause marked acute discomfort and physiological alterations.

Supported by US Army Med Res Materiel Cmd, DAMD17-96-C-6127.

Appendix 3-L

Submitted for Experimental Biology (FASEB) meeting, San Diego, CA, April 2000

Fluid redistribution and acute mountain sickness (AMS)

Roach R.C., K. Riboni, D.P. Maes, M. Icenogle and J.A. Loeppky.

AMS strikes those that ascend to high altitude (HA) too high and fast. The symptoms include headache, nausea and lassitude. Fluid retention/redistribution and relative hypoventilation have been proposed as significant factors in AMS pathophysiology, but the fundamental causes of the illness remain a mystery. As part of a larger study to examine the role of gender in AMS, we identified subjects that either developed severe AMS as judged by the ESQ AMS-C score (AMS, n=15, score 2.9±0.1) or remained free from the illness (N-AMS, n=15, score 0.1±0.0). Subjects were studied at baseline (BL; 635 mmHg) and during 12 hr at simulated HA (A1 to A12; 4800 m; 426 mmHg). Measurements included PaO_2; $PaCO_2$; resting minute ventilation (V_E); fluid intake and urine volume (fluid i-o); plasma volume (PV; Evan's Blue); extracellular water (ECW; sodium bromide) and total body water (TBW; deuterium oxide). PaO_2, $PaCO_2$ and V_E were similar in AMS and N-AMS at BL and simulated altitude. From BL to A12: ECW rose 27% in AMS and fell 3.4% in N-AMS ($p<0.05$); PV fell 6% AMS vs. 13% in N-AMS ($p<0.05$) and TBW rose in AMS vs. N-AMS ($p=0.06$). These findings show coincident AMS and expansion of the ECW at A12. The fluid shift may have preceded development of AMS. Fluid i-o was steady in AMS from BL to A12. In contrast, in N-AMS a 150±33ml/hr diuresis was observed in the first 3-hrs at HA ($p<0.05$). These data suggest that a lack of a diuresis in the first few hrs at HA is related to the onset of AMS. Elucidation of the relationship between the lack of diuresis to fluid redistribution awaits serial measurements of fluid compartments during the early hrs of HA exposure.

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Appendix 3-M

Submitted for American College of Sports Medicine Meeting, Indianapolis, Indiana, May 2000

DECLINE IN FOOD INTAKE DURING ACUTE ALTITUDE EXPOSURE IS NOT ALTERED BY MENSTRUAL CYCLE PHASE.

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Recent data demonstrate increased food intake during the luteal phase of the menstrual cycle. Less evidence supports the common belief that oral contraceptives increase appetite and weight gain. In contrast, high altitude exposure and acute mountain sickness (AMS) can lead to reduced food consumption. Thus, luteal phase and oral contraceptive use might attenuate the hypophagia of AMS. We examined food consumption and symptoms of AMS (AMS-C score) during a 12-hr exposure to simulated high altitude (16,000 ft, barometric pressure 426 mm Hg). Women were studied in the luteal (L) and follicular (F) phases of the menstrual cycle or while taking oral contraceptives (Pill or Placebo). Men were studied once in an identical protocol. For one control day and the following experimental day they were provided 106\% of the average caloric intake they reported in a 3-day dietary record. Foods not eaten were recorded and differences between nutrients consumed on the day at altitude and the day prior to altitude were calculated. The mean decline in total calories varied among the five groups, with no significant between-group differences (28\%, 14\%, 23\%, 31\% for women in the F, L, Pill, Placebo groups respectively, and 14\% for men). AMS-C scores were similar among groups. The decline in total calories was related to AMS severity in men (n=18; r=0.55) and women in F (n=15; r=0.73) and L (n=15; r=0.61, p$<$0.05 for those 3 groups). However, this relationship was not significant among women taking oral contraceptives, Pill (n=18; r=0.35, p=0.15) and Placebo (n=18; r=0.40, p=0.10). Mechanisms by which oral contraceptives may weaken the relationship between symptoms of illness and decreased food intake require further study. We conclude that orexic drive in the luteal phase does not attenuate AMS-induced hypophagia. Supported in part by US Army Med Res Material Cmd, DAMD 17-96-C-6127.

Appendix 4

LIST OF PERSONNEL RECEIVING PAY FROM THE RESEARCH EFFORT

(ALPHABETICAL)

John Adams

Arvind Caprihan, Ph.D.

Carole Conn, Ph.D.

Benito Dutcher

Peter Hackett, M.D.

Helmut Hinghofer-Szalkay, M.D.

Lauren Icenogle

David Kilgore

Dean Kuethe, Ph.D.

Jack Loeppky, Ph.D.

Kris Loeppky

Damon Maes

Rob Roach, Ph.D.

Katrina Riboni

Darleen Sandoval

Pietro Scotto, M.D.

Greg Shaw

Simon Strickling

51 subjects (see Form 60-R for each, included in this mailing)